CONTENTS

# The American Journal of Medicine

VOL. VII OCTOBER, 1949 No. 4

## *Editorial*



## *Clinical Studies*



*Contents continued on page* 5

[redacted]

safe and effective reduction
of elevated blood cholesterol
with lipotropic therapy

"Clinical and experimental observations indicate that lipotropic factors [choline, methionine and inositol] . . . prevent or mitigate the deposition of cholesterol in the vascular walls of rabbits and chickens and seem to exert a decholesterolizing effect on atheromatous deposits in man, chickens and rabbits."*

These findings suggest the therapeutic possibilities of lipotropic Methischol in the prevention and possible treatment of atherosclerosis.

# methischol®

*Suggested daily therapeutic dose of*
*3 tablespoonsful or 9 capsules contains:*

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|---|---|
| *Choline Dihydrogen Citrate* (*Choline . . . 1 Gm.*)* | *2.5 Gm.* |
| *dl-Methionine* | *1.0 Gm.* |
| *Inositol* | *0.75 Gm.* |
| *Liver Fractions from* | *36.0 Gm. liver* |
| **present in syrup as 1.15 Gm. choline chloride* | |

*Supplied in bottles of 100, 250, 500 and 1000 capsules, and 16 oz. and one gallon syrup.*

**methischol**

*combines major lipotropic agents*
*for specific therapy in reparable liver damage . . . cirrhosis,*
*fat infiltration, functional impairment,*
*toxic hepatitis, infectious hepatitis.*

write for samples and literature

u. s. vitamin corporation
casimir funk laboratories, inc. (affiliate)
250 east 43rd st., new york 17, n. y.

*Hueper, W. C.: Medical Clinics of North America, May 1949.

CONTENTS

# The American Journal of Medicine

VOL. VII OCTOBER, 1949 No. 4

*Contents continued from page* 3



*Contents continued on page* 7

# *when* MIGRAINE *attacks*

***FIRST EFFECTIVE***

***oral* TREATMENT**

***OF MIGRAINE ATTACK***

Sandoz proudly announces the *first effective oral* treatment of migraine—

Clinical investigation[1] demonstrated that 80% of a series of cases experienced good results. Best results were obtained in migraine, histamine and tension headaches.

Friedman,[2] in a large series of migraine cases, found Cafergone 55% more effective than ergotamine tartrate alone.

Later reports[3, 4] were equally favorable.


1. Horton, B.T., Ryan, R. E. & Reynolds, J. L., Proc. Staff Meet. Mayo Clinic, 23:105, Mar. 3, 1948.
2. Friedman, A. P., N. Y. State Jl. of Med. (in press).
3. Ryan, R. E., Postgraduate Medicine (in press).
4. Hansel, F. K., Annals of Allergy (in press).


# Cafergone

SANDOZ®

(ergotamine tartrate 1 mg.; caffeine 100 mg.)

(Experimentally identified as E.C. 110)

*Originality • Elegance • Perfection*

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CONTENTS

# The American Journal of Medicine

VOL. VII OCTOBER, 1949 No. 4

*Contents continued from page 5*

## *Clinico-pathologic Conference*



## *Case Reports*

# General Information

THE AMERICAN JOURNAL OF MEDICINE extends an invitation to the profession for original releases on clinical investigations, clinical reviews, case reports and articles designed for postgraduate teaching.

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Change of address must reach us by the 15th of the month preceding month of issue.

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*Text.* Manuscripts are to be typewritten on one side of the paper, with double spacing and good margins. The original should be sent to the editor and a carbon copy retained by the author.

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*Bibliographies.* Bibliographic references should be at the end of the manuscript and not in footnotes. Each reference should include the following information in the order indicated: Name of author with initials; title of article; name of periodical; volume, page and year. The following may be used as a model:

BANCROFT, F. W., STANLEY-BROWN, M. and QUICK, A. J. Postoperative thrombosis and embolism. *Am. J. Surg.*, 26: 648, 1945.

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# compare

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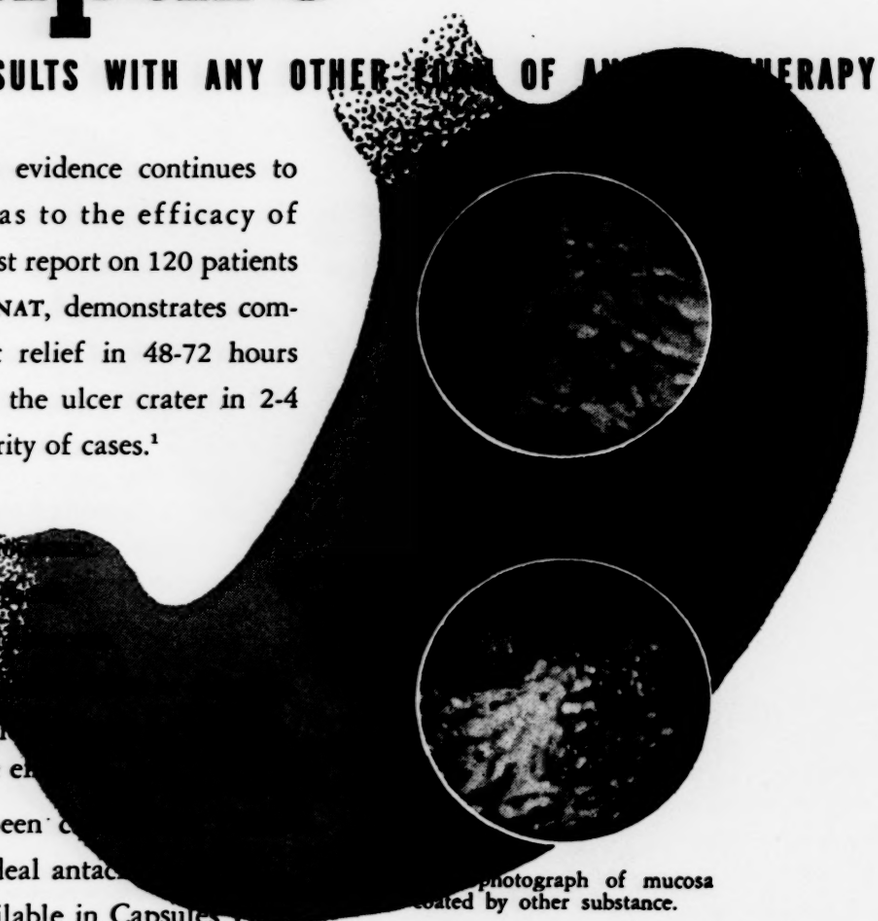
Mounting clinical evidence continues to support claims as to the efficacy of **RESINAT.** The latest report on 120 patients treated with **RESINAT,** demonstrates complete symptomatic relief in 48-72 hours and regression of the ulcer crater in 2-4 weeks in the majority of cases.[1]

**RESINAT:**

1. Is completely [illegible]
2. Acts as an adso[illegible]
3. Coats the ga[illegible]
4. Does not ca[illegible]
5. Produces no ac[illegible] jectionable side e[illegible]

**RESINAT** has been [illegible] approach to the ideal antac[illegible]

**RESINAT** is available in Capsules [illegible] Gm.), Tablets (0.5 Gm.), Powder (1 Gm.).



[illegible]photograph of mucosa [illegible]oated by other substance.

Weiss, S., Espinal, R.B. & Weiss, J.: Therapeutic Application of Anion Exchange Resins in the Treatment of Peptic Ulcer, Review of Gastroenterology, 16:501-509, June, 1949.

# RESINAT

RESINAT PATENT PENDING

*Literature and samples available*

*completely nontoxic anion exchange resin*

## FOR PEPTIC ULCER

THE NATIONAL DRUG COMPANY, PHILADELPHIA 44, PA.

*Manufacturers of*

***Pharmaceutical, Biological and Biochemical Products for the Medical Profession***

# now, better relief with...

## a distinctive, new, non-narcotic antitussive-expectorant

At last, something really new in cough syrups . . . something completely rational . . . clinically sound . . . Robitussin 'Robins'. Robitussin employs glyceryl guaiacolate and desoxyephedrine hydrochloride, in a palatable aromatic syrup vehicle.

Glyceryl guaiacolate has proven an effective aid to expectoration, and a cough ameliorator with prolonged action, through its increase in and thinning of respiratory tract fluid;[1,2,3] yet it has no ill effect upon digestion.[1]

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The syrupy vehicle, with its aromatic volatile oils, has a local demulcent effect. Furthermore, it assures patient cooperation by providing a base which makes Robitussin one of the most palatable of all antitussive-expectorants.

You will find Robitussin 'Robins' an exceptionally efficient, safe, therapeutic tool in the management of cough—for both adults and children.

# Robitussin

rationally formulated!

clinically proved!

Robins

**FORMULA**: Each 5 cc. (1 teaspoonful) of Robitussin contains:
Glyceryl Guaiacolate . . . 100 mg.
Desoxyephedrine Hydrochloride . . . 1 mg.
In a palatable aromatic syrup.

**DOSAGE**: Children: one-half to one teaspoonful, according to age, three or more times daily. Adults: one or two teaspoonfuls, as necessary every two to three hours.

**SUPPLIED**: Pint and gallon bottles.

**REFERENCES**: 1. Connell, W. F. et al: Canadian Med. Assoc. J., 42:220, 1940. 2. Perry, W. F. and Boyd, E. M.: J. Pharm. Exper. Ther., 73:65, 1941. 3. Stevens, M. E. et al: Canadian Med. Assoc. J., 48:124, 1943. 4. Foltz, E. E. et al: J. Lab. Clin. Med., 28:603, 1943. 5. Graham, B. E.: Ind. Eng. Chem., Ind. Ed., 37:149, 1945. 6. Schulz, F. and Deckner, S.: Klin. Wochschr., 21:674, 1942.

**ROBITUSSIN—For *Rational* Cough Management**

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# OPTIMUM ANTI-ANEMIA RESPONSE

VITAMIN $B_{12}$, isolated in the Merck Research Laboratories, is available as Cobione* (Crystalline Vitamin $B_{12}$ Merck). Cobione has been proved by clinical studies to exert high hematopoietic activity in the treatment of

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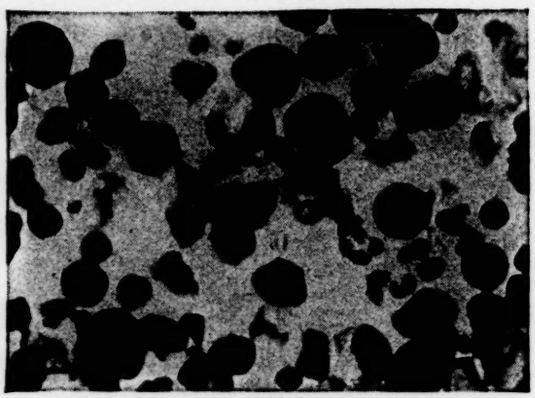
- ★ **SPRUE (tropical and nontropical)**

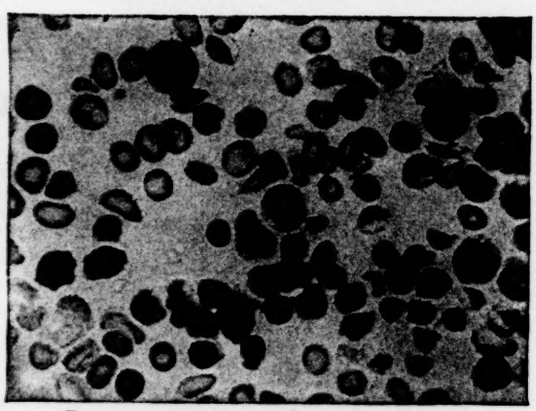


*Smear showing megaloblastic bone marrow of patient with pernicious anemia before treatment with Cobione*

**COBIONE:**

- **A crystalline compound of extremely high potency.**
- **Effective in extremely low doses, because of its high potency.**
- **May be administered subcutaneously or intramuscularly in precise dosage.**
- **No known toxicity in recommended dosages.**
- **Supplied in ampuls of 1 cc. of saline solution of Cobione, each cc. containing 15 micrograms of Crystalline Vitamin $B_{12}$.**

***Literature available on request.***



*Bone-marrow smear from same patient ninety hours after a single injection of 0.025 mg. of Cobione*

**Cobione is the trademark of Merck & Co., Inc. for its brand of Crystalline Vitamin $B_{12}$.*

$B_{12}$

MERCK

**MERCK & CO., Inc.** *Manufacturing Chemists* **RAHWAY, N. J.**

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protection
of
**rutin**
the
action
of
**aminophylline**
the
sedation
of
**phenobarbital**
—for
use
in
selected
cardiovascular
and
diabetic
conditions
in
which
excessive
capillary
fragility
presents
a
complicating
hazard
—bottles
of
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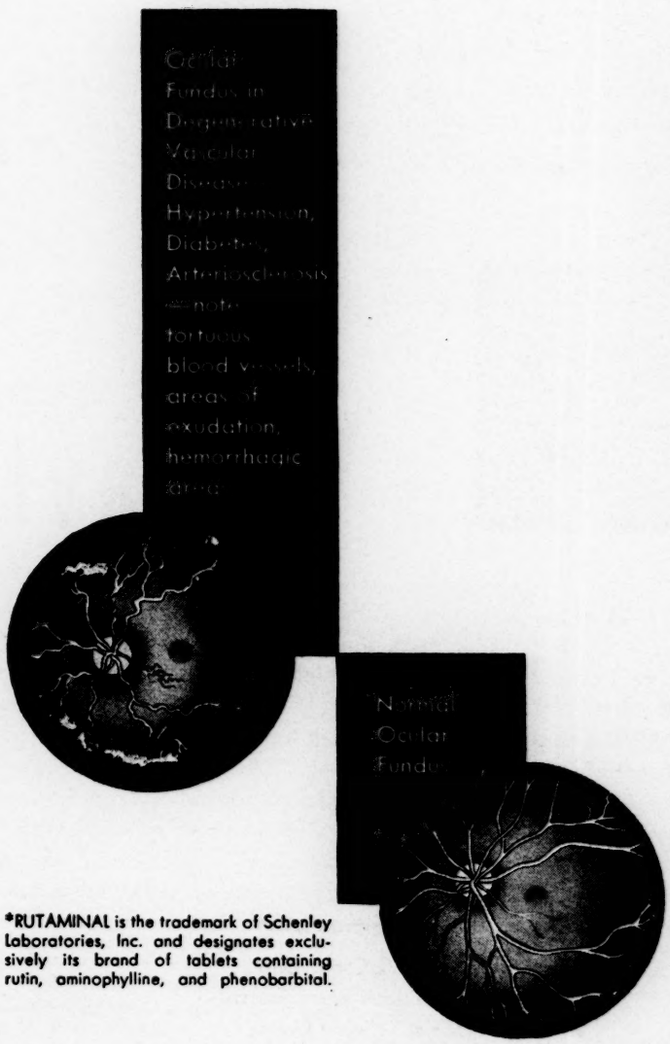
tablets

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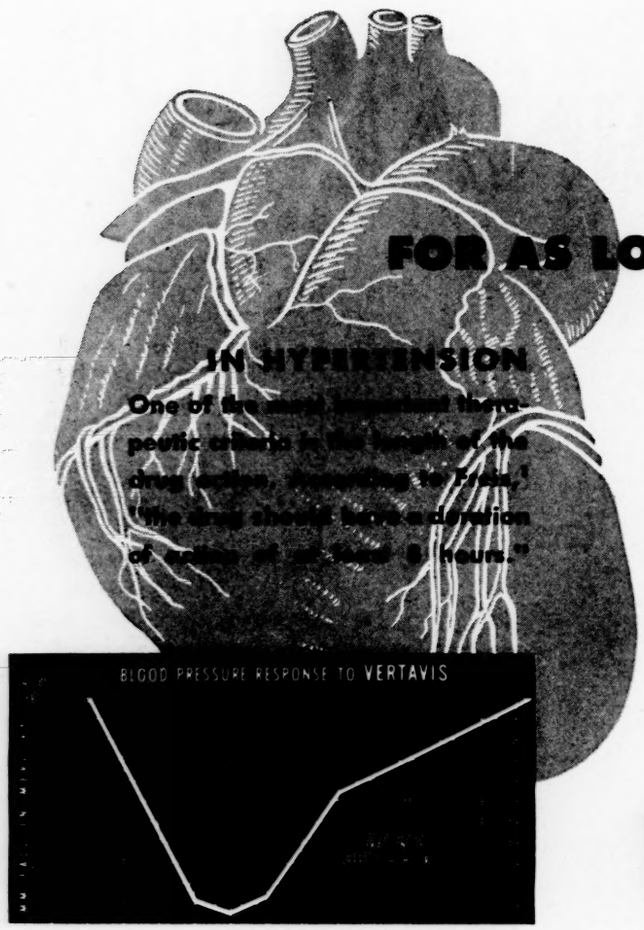
**schenley** laboratories, inc., 350 fifth ave., new york 1, n. y.




# FOR AS LONG AS 14 HOURS

## IN HYPERTENSION

One of the most important therapeutic criteria in the length of the drug action. According to Freis, "the drug should have a duration of action of at least 8 hours."

# Vertavis®

VERTAVIS is the only drug, of all the hypotensive agents tested, which meets this criterium—in fact, the duration of action of VERTAVIS is *as long as 14 hours.* According to clinical investigations, the hypotensive effect of VERTAVIS "usually begins in one or two hours, reaches a maximum in four to six hours, and ends in ten to fourteen hours."[1,2,3]

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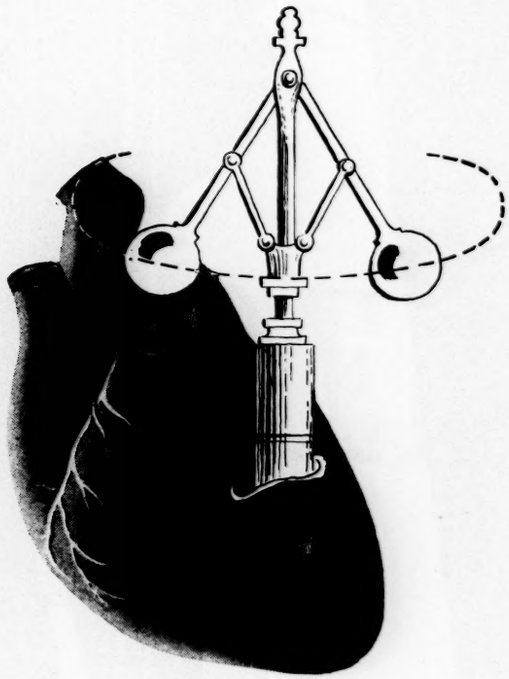
*Supplied:* Vertavis 10 Craw Units
Vertavis with Phenobarbital
Vertavis 5 Craw Units
In bottles of 100, 500, 1000.

1. Freis, E. D.: Med. Clin. N. Am. 32: 1247-1258, 1948.
2. Freis, E. D., and Stanton, J. R.: Am. Heart J. 36: 723-738, 1948.
3. Barker, H., et al: Paper Presented before Am. Coll. Phys., Chicago, May, 1947.

**IRWIN, NEISLER & CO.** 63rd YEAR Irwin **DECATUR, ILLINOIS**



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When Nativelle isolated Digitaline, he eliminated the non-absorbable glycosides of the whole leaf... thus virtually *ending untoward side reactions* in digitalization and maintenance. Digitalization became a matter of hours, not days. *Maintenance became positive* because absorption was complete and the uniform rate of dissipation afforded full digitalis effect between doses.

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**Chief active principle of digitalis purpurea* (digitoxin)**

**Not an adventitious mixture of glycosides, just the purified chief active principle.*

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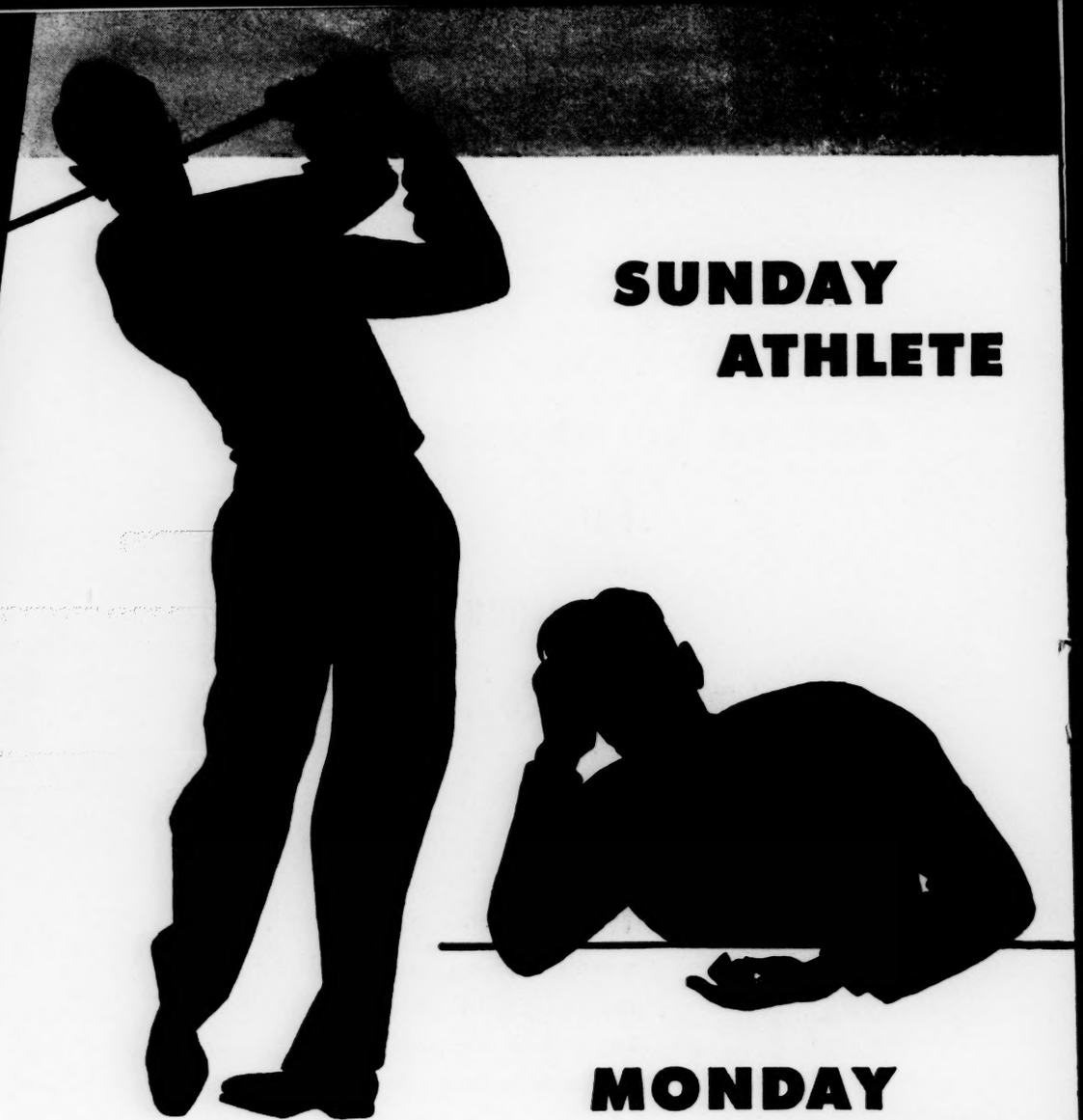
**RAPID DIGITALIZATION:** 1.2 mg. in equally divided doses of 0.6 mg. each at three-hour intervals.



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As effective against the Sunday-athlete's pain and stiffness as it is against the distress of rheumatic and allied disorders, Arthralgen provides rapid, sustained relief of discomfort and disability.

Vasodilatation with methacholine chloride, rubefaction with thymol and menthol, analgesia with methyl salicylate—all contribute to the effective, prolonged action of Arthralgen.

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***Arthralgesic Unguent***

for quick relief of joint
and muscle pain

**Containing no histamine, Arthralgen does not cause itching or whealing of the skin. Convenient to use, its uniquely elegant ointment base is easily washable.**

**Arthralgen is available in 1-ounce collapsible tubes and half-pound jars.**

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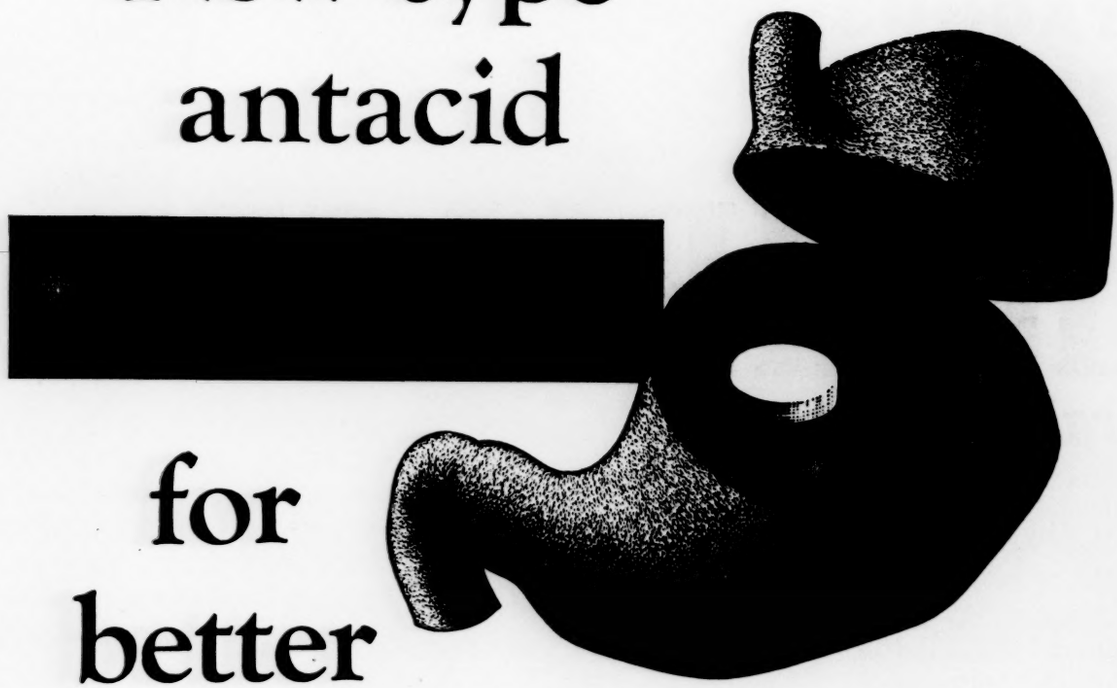
# New type antacid



# for better management of peptic ulcer

## Carmethose gives prolonged control with no adverse effects

Carmethose promptly lowers gastric acidity, and its protective tenacious coating has been observed in the stomach for as long as three hours.[1]

Adult dose is 2 to 4 tablets or teaspoonfuls 4 times daily between meals.

**Carmethose Tablets:** *sodium carboxymethylcellulose, 225 mg. and magnesium oxide, 75 mg. Bottles of 100*

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**Ciba**

PHARMACEUTICAL PRODUCTS, INC., SUMMIT, NEW JERSEY

CARMETHOSE—Trade Mark 2/1504M

**Advantages over adsorbent gels:**

1. *Non-constipating*—hydrophilic gel promotes normal elimination.[1, 2]
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3. *Palatable*—small, easily swallowed tablets and pleasantly flavored liquid—preferred by patients.[2]

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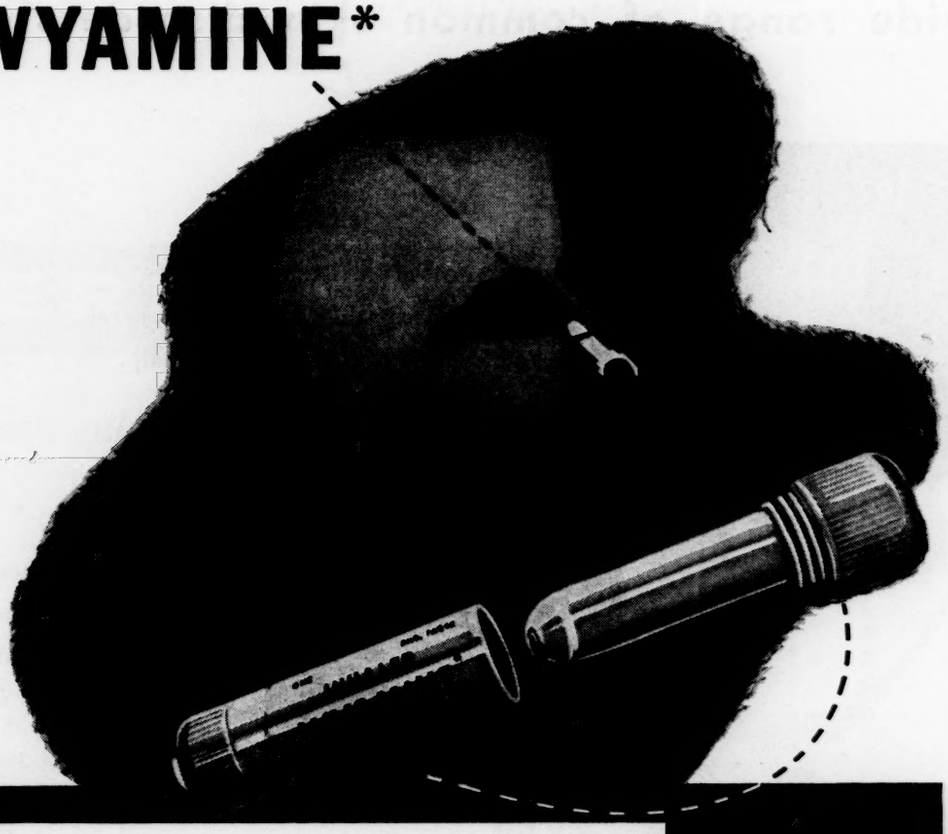
1. *No acid rebound*—effectively inhibits acid-pepsin activity, with no secondary hypersecretion.
2. *Protective coating*—mucin-like gel is rapidly formed and clings to ulcer crater and gastric mucosa.
3. *Non-systemic*—cannot disturb acid-base balance because it is non-absorbable.

1. Brick, I.B.: Amer. J. Dig. Dis., *In Press* 2. Bralow, Spellberg & Necheles: Scientific Exhibit #1112, A.M.A. Annual Session 1949

# WYAMINE*



The action of WYAMINE is so effective that the nasal passages clear up almost immediately after two or three inhalations from the Inhaler in each nostril. And the remarkable feature of Wyamine is that this medication can be used just before retiring without disturbing a pleasant night's rest . . . maximum efficacy with minimum stimulation.

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*Trademark, brand of Mephentermine (N-methyl-phenyl-tertiary butylamine)

to clear nasal congestion without discomfort •

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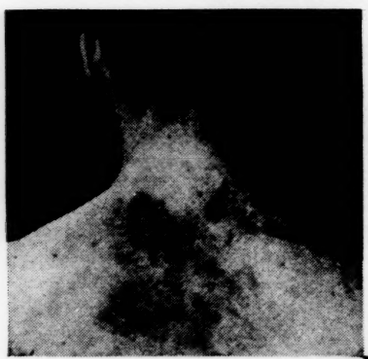
Wyeth®

# highly effective in an unusually wide range of common skin disorders



**Pragmatar** is particularly useful in seborrheic dermatitis, and in the general care and hygiene of the seborrheic scalp.

**Pragmatar** often brings dramatic improvement in the common fungous infections—even in "athlete's foot."

**Pragmatar** is extremely valuable in eczematous eruptions, especially those in which a seborrheic factor is involved.

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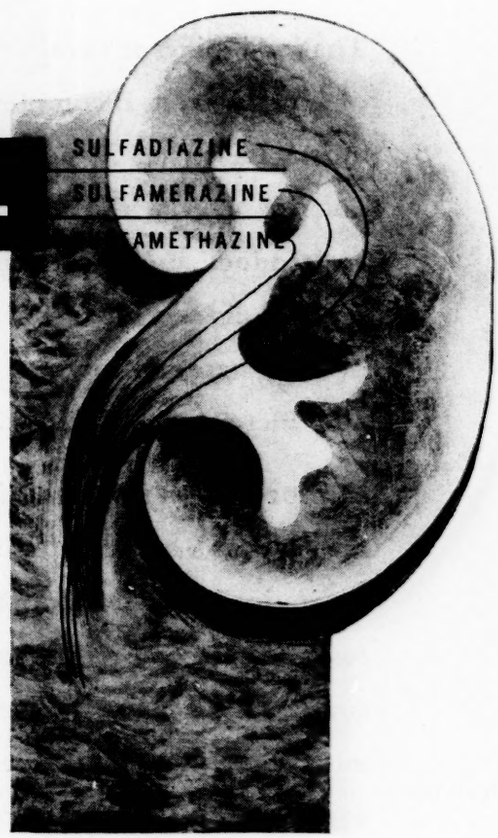
# Pragmatar

**the outstanding tar-sulfur-salicylic acid ointment**

# *New Sulfa Combination...*

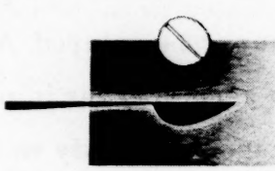
## TERFONYL

*for safe sulfonamide therapy*




**HIGH BLOOD LEVELS**
**All three components are absorbed and excreted independently. High blood levels can be maintained without kidney concretion and with minimal sensitivity reactions.**

**WIDE ANTIBACTERIAL RANGE**
**All three components have a wide antibacterial range and are highly effective in the treatment of pneumonia and other common infections.**



**0.5 Gm. tablets**
**Bottles of 100 and 1000**
**Suspension, 0.5 Gm. per cc.**
**(pleasant raspberry flavor)**
**Pint bottles**



**SQUIBB** MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858

# The Importance of Meat To Your Geriatric Patients

That a significant number of elderly persons suffer from a deficiency of protein, iron, B complex vitamins, and calcium is the consensus of most geriatrists. Depending upon the extent and duration of these nutrient deficits the well-being and stamina of the individual are undermined, not infrequently to the point where the presence of organic disease may be suspected. Furthermore, nutrient deficiencies of long standing lower resistance to infectious disease and appreciably increase the hazards of surgery.

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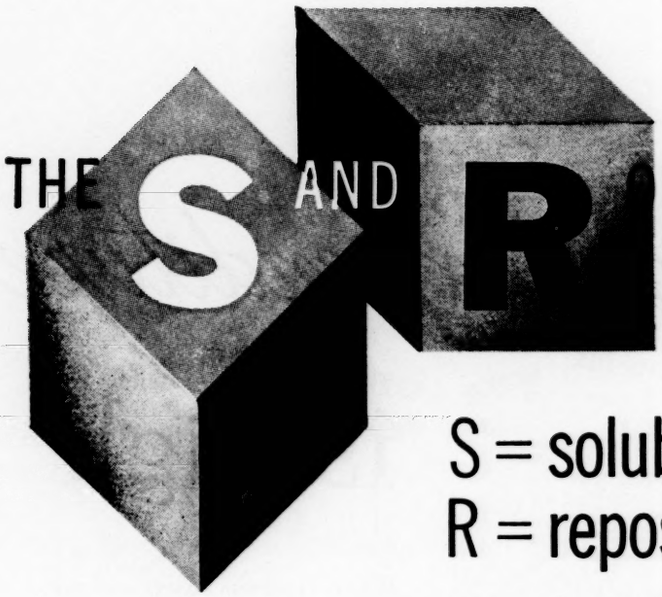
The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.


**American Meat Institute**
**Main Office, Chicago...Members Throughout the United States**

# THE S AND R OF PENICILLIN S-R
TRADE MARK




## S = soluble
## R = repository

Two forms of penicillin combined to
give the inherent advantages of both

### PENICILLIN S-R ALSO MEANS SPEEDY RISE

of blood penicillin level—twenty times higher than procaine penicillin in oil—within a half hour or less.

### PENICILLIN S-R MEANS SUSTAINED RESPONSE

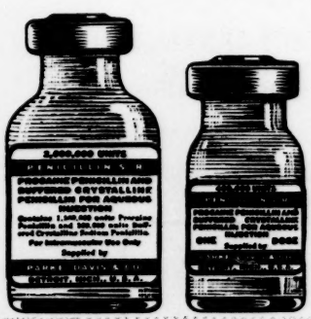
to a 1 cc. intramuscular injection—prolonged effective levels for 24 hours or longer.

### PENICILLIN S-R MEANS SLOW AND RAPID

absorption from the Parke-Davis combination of procaine penicillin (controlled crystal size), 300,000 units, and buffered soluble penicillin, 100,000 units.

### PENICILLIN S-R MEANS SIMPLIFIED ROUTINE

in penicillin therapy—no oil, wax or suspending agents to impede injection and clog syringe and needle. Prepared with aqueous diluent, PENICILLIN S-R needs no vigorous shaking and flows freely



### PENICILLIN S-R

is supplied in one-dose (400,000 units), five dose (2,000,000 units), and ten-dose (4,000,000 units) vials. When diluted according to directions, each cc. contains 300,000 units of crystalline procaine penicillin-G and 100,000 units of buffered crystalline sodium penicillin-G. The one-dose vial is also available, if desired, with an accompanying ampoule of Water for Injection, U. S. P.

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When vigorous sports and outdoor activities increase caloric energy requirements, candy proves nutritionally advantageous as well as satisfying. It yields its contained carbohydrate promptly, permits of rapid replenishment of depleted or lowered glycogen stores, and aids the organism in recovering from fatigue. Furthermore, virtually everyone likes candy, making it particularly enjoyable when energy expenditure is high during fall and winter.

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*Council on Candy*

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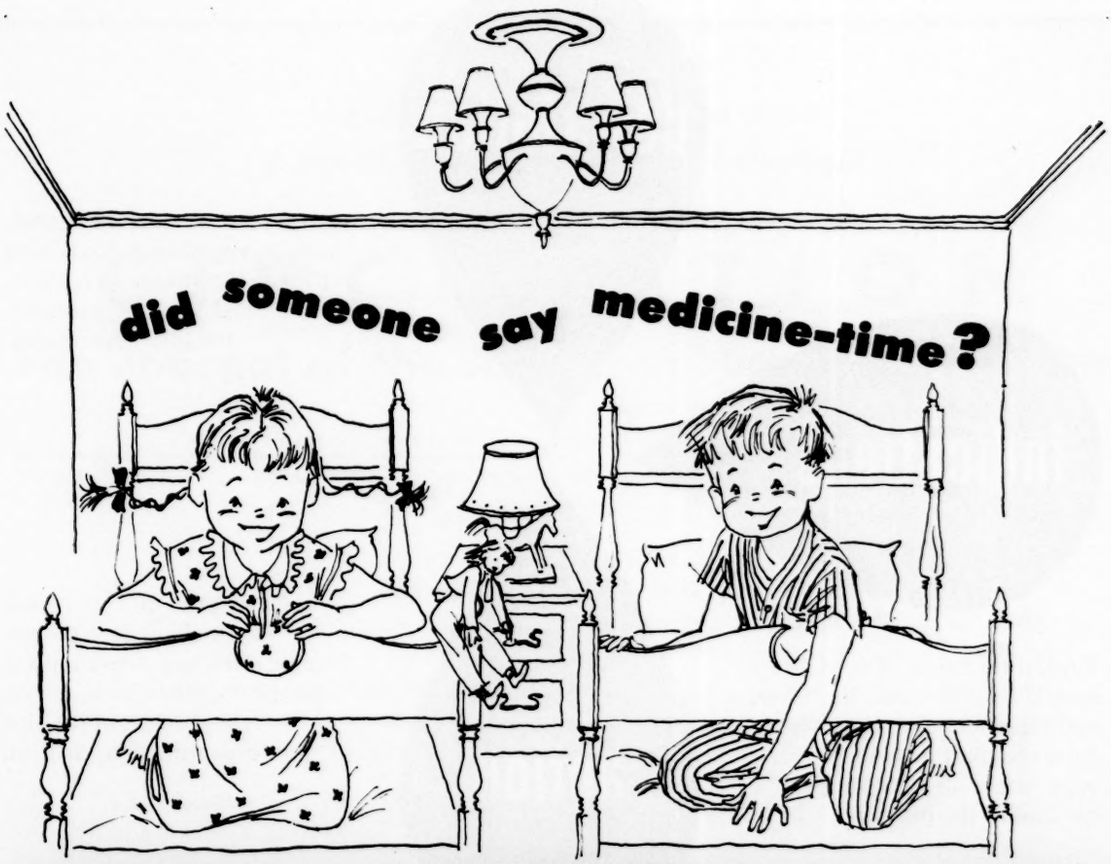


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The American Journal of Medicine

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# Editorial

## Treatment of Auricular Flutter with Digitalis

THE use of digitalis in auricular fibrillation has been clearly defined on a rational basis for many years. Every doctor is familiar with the principle of slowing the ventricle by means of this drug, and all agree on the need of maintaining a slow ventricular rate by adequate continuous dosage. Restoration of normal mechanism is not usually anticipated and should it occur is regarded as a coincidence or perhaps the result of improved cardiac function. It is confusing, therefore, to find in most discussions of the treatment of auricular flutter—a condition so closely related to fibrillation—an entirely different prescription for the use of digitalis. It is the fact that this prescription, obviously obsolete, is still given in some widely used recent textbooks which prompts the following remarks.

The procedure, as described, is essentially as follows: Digitalis is given in large doses until the ventricle is slowed just as in cases of fibrillation. The drug is continued up to the point of tolerance, whereupon within a few days flutter may be expected to pass over to fibrillation. But now instead of continuing digitalis the drug is stopped altogether, whereupon a normal mechanism is said often to supervene within a few hours or days. It should be emphasized that the crucial point in the prescription is the stopping of digitalis as soon as fibrillation comes on; it is implied that continued administration of the drug at this point may prevent the return of a normal mechanism. Inasmuch as this prescription is so directly at variance with the established usage of digitalis in auricular fibrillation, one must examine the results which have been obtained with it as well as its theoretic validity.

It appears that the first to suggest for auricular flutter the procedure outlined above (in future referred to as the "classical therapy") was Sir Thomas Lewis in his paper of 1912.[1] In the case described in detail digitalis was given until 4:1 block and later auricular fibrillation supervened. Digitalis was stopped but after eight days fibrillation was still present. Two weeks later the patient was found to have a normal mechanism. It was in a subsequent paper,[2] however, that Lewis described more cases and became more emphatic in defining the "classical therapy." He concluded that "Even when it has been present many months, flutter may often be abolished by the administration of digitalis. This drug induces temporary fibrillation and (if digitalis is stopped) the normal rhythm is subsequently restored and may persist." In the following year Ritchie[3] in his book on auricular flutter reported other cases in which the classical procedure was used. Ritchie remarked (p. 107) that "the fourth phase (of digitalis effect) is characterized by restoration of physiological rhythm. In some instances this may occur while the

[1] LEWIS, T. Observations upon disorders of the heart's action. *Heart*, 3: 279, 1911–1912.

[2] Idem. Observations upon a curious and not uncommon form of extreme acceleration of the auricle. *Heart*, 3: 171, 1912–1913.

[3] RITCHIE, W. T. Auricular Flutter. Edinburgh and London, 1914. W. Green & Co.

patient is still taking digitalis but as a rule not until the drug has been discontinued." . . . The restoration of the normal rhythm has been observed as early as the third or as late as the 23rd day after the patient has ceased taking digitalis."

It is of interest that the eight cases upon which the classical therapy is based do not really seem to give it strong support. First, flutter does not go over to fibrillation with any regularity. In the eight cases three failed altogether to fibrillate and in a fourth digitalis was given for a year before fibrillation supervened. In two more cases normal rhythm was not restored when digitalis was withdrawn. In only three of the eight cases did the prescribed sequence of events really unfold itself, and in these the interval between cessation of digitalis and resumption of normal mechanism varied greatly.

Ritchie[3] in his final discussion of treatment (pp. 130–136) seems not entirely satisfied with the classical procedure. He points out that it worked in about only one-half of the cases and that even then there was likely to be a return to flutter or to fibrillation. He raises the question of whether just enough digitalis to control the ventricular rate may not be better therapy than the large doses which are supposed to induce fibrillation.

Our own experience gives no support to the theory or practice of the classical therapy. We have seen patients with auricular flutter revert to a normal mechanism without any digitalis and with or without a recognized intervening period of fibrillation. Some patients have gone back to normal mechanism while on digitalis.

Flutter should therefore be treated with digitalis on the same basis as fibrillation. Should flutter go over to fibrillation, the drug should not be stopped but continued in order to keep the ventricle slow just as in any instance of auricular fibrillation. There is no formula whereby return of normal mechanism can be regularly induced by the use of digitalis, and quinidine should be used if prompt restoration is to be attempted.

ARTHUR L. BLOOMFIELD, M.D.

# Clinical Studies

## Some Effects of Digoxin upon the Heart and Circulation in Man*

### *Digoxin in Left Ventricular Failure*

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*New York, New York*

THE advent of the catheterization technic has not only prompted investigation of the hemodynamics of cardiac failure but also has stimulated renewed interest in the study of cardiovascular drugs in man. The entire problem of cardiac insufficiency is at present being re-examined in many clinical laboratories. Beyond differentiating high output and low output types of cardiac failure, little has been done to define in detail the complexity of the physiopathologic factors which may be involved in a single case. This definition is not only important to the better understanding of cardiac abnormalities but is crucial in any pharmacologic investigation. Therefore, it has become increasingly evident that a detailed analysis of both the clinical and physiologic status of the patient at the time of the drug study is essential. When the hemodynamic pattern is well defined, this analysis contributes much to the understanding of the natural history of certain disease processes and the subsequent physiologic alterations produced thereby. In addition it may afford the opportunity of isolating groups of cases with similar physiopathology.

Drug effects are frequently clarified when studied in groups of patients with similar hemodynamic patterns. The majority of investigations on the effect of digitalis preparations have been carried out in patients with advanced heart disease in whom the physiologic alterations are mutually dependent one upon another and are numerous and complex and variable from one patient to another. In such cases it is often difficult to assess the exact mode of action of the drug. If, however, a group of patients is found in which the altered hemodynamics spring from a simple rather than a complex physiologic abnormality and the number of variables is minimal, a more precise delineation of the action of a drug on the circulation can be attempted.

Patients with pure left-sided heart failure comprise such a group. This type of case is difficult to find and hence this report includes observations on only five patients treated with digoxin. In order to elucidate the hemodynamic responses observed when left ventricular failure is relieved by medication an additional case of a patient with left ventricular failure treated with quinidine is presented. As a contrast the effect of digoxin in one case of chronic cor pulmonale in congestive heart failure, chosen from a group of patients currently being studied, is discussed. The latter case illustrates the reaction of the circulation to digoxin when an entirely different state exists, namely, pure right-sided failure.

* From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Cardiopulmonary Laboratory of the First Medical and Chest Services (Columbia University Division), Bellevue Hospital, New York, N. Y. The work described in this paper was supported by a grant from the Life Insurance Medical Research Fund, with additional support provided by the Commonwealth Fund.

## MATERIAL AND METHODS

The six patients with left-sided failure include three with hypertensive cardiovascular disease, one with hypertensive cardiovascular disease and arteriosclerotic heart disease and two with rheumatic heart disease. The criteria used for diagnosis were those of the American Heart Association. The functional and therapeutic classification represents the status of the patient at the time of the study. It is worthy of comment that five of these patients had symptoms of paroxysmal nocturnal dyspnea, orthopnea and exertional dyspnea in varying degrees of severity but none had pulmonary rales or rhonchi. Of the five patients with symptoms four had an apical diastolic gallop. The patient receiving quinidine had been digitalized and had neither symptoms, signs nor gallop rhythm, but the hemodynamic studies revealed pulmonary hypertension, presumably due to left-sided heart failure.

The method of investigation used in this study was similar to that discussed in a previous report[1] with the exception that no sedation was used. A control electrocardiogram, including six precordial V leads and the augmented unipolar limb leads, was taken before introduction of the catheter and the intra-arterial needle. In all of these cases a double lumen catheter was used. This type of catheter permits registration of both right ventricle and pulmonary artery pressure curves throughout the study, eliminating further manipulation of the catheter once it is properly located. No attempt was made to secure right auricular mean pressures since the right ventricular end diastolic pressure is a better indication of the filling pressure of the right heart. Pressure curves were recorded by Hamilton manometers and analysis of them has been amply described previously.[1] A control cardiac output[2,3] and blood volume determinations[4] were done before administration of digoxin. All mixed venous blood samples were drawn from the pulmonary artery. Digoxin, 1.0 to 1.5 mg. in 30 cc. of physiologic saline, was injected through the catheter into the pulmonary artery over a five-minute period. Blood pressures were recorded at the conclusion of the injection and every ten to fifteen minutes for one to one and one-half hours thereafter. Two subsequent cardiac output determinations were made. The study was concluded with a second complete electrocardiogram. Heart rate was computed from the electrocardiogram which was taken continuously on lead II. Total peripheral resistance was calculated as previously described.[1]

It is obvious that maintenance of the patient in a constantly steady state is essential to this type of study. Any untoward reaction noted during the procedure demands correction of the underlying cause or immediate cessation of the investigation. A note of caution should be struck here concerning cardiac arrhythmias during catheterization. As was just mentioned the electrocardiogram was observed constantly throughout the study. Manipulation of the catheter tip in the tricuspid area and within the right ventricle frequently causes ventricular premature contractions to appear. In one hundred cardiac patients catheterized over a period of eighteen months transient right bundle branch block appeared during the procedure in two cases and the block disappeared as soon as the catheter was removed from the cavity of the right ventricle. Manipulation of the tip of the catheter in the region of the interventricular septum, especially at the outflow tract, may produce short runs of ventricular tachycardia. It is therefore inadvisable to leave the free tip of the catheter in the right ventricle for any length of time or to manipulate it back and forth across the pulmonic valve; hence the advantage of the double lumen catheter. The arrhythmias are not only in themselves potentially dangerous to the patient but radically alter the dynamics of the circulation, causing both blood pressure and cardiac output to change. In this group of one hundred cardiac patients no serious complications ensued from the catheterization procedure as a result of the strict precautions taken.

In any evaluation of changes produced by medication it is important to ascertain the range of variation expected with the technics employed—in this instance, the catheterization procedure. Ideally, such data should be obtained in a group of patients undergoing the same procedure but to whom no drug was given. In addition data could be obtained during control periods preceding administration of the drug. Tables I and II contain data on cardiac output determinations obtained in the former manner while in Table III are tabulated the blood pressure variations observed in a peripheral artery and in the right heart during the control periods before medication was given.

Control figures, shown in Table I, have been obtained by analyzing statistically the data on two separate and successive measurements of cardiac output in all the patients who had been studied solely for diagnostic reasons over the same eighteen-month period during which the digoxin studies were pursued. None of these patients had congenital heart defects. They were studied by three different catheterization teams using the same laboratory and essentially the same procedure. None of these patients received any drug during the study nor were they subjected to any other procedures, such as pressure breathing or exercise. The average time between the first and second determinations was twenty-seven minutes and the length of time the patient was on the fluoroscopic table before the second determination was made averaged two and one-half hours.

TABLE I

STATISTICS OF TWO SUCCESSIVE DETERMINATIONS OF CARDIAC OUTPUT IN TWENTY CONTROL PATIENTS NOT RECEIVING MEDICATION

| | First Determination | | | Second Determination | | |
|---|---|---|---|---|---|---|
| | Mean | S.E. | Range | Mean | S.E. | Range |
| Oxygen consumption, cc./min./M.$^2$ | 140 | ±2.6 | 158–107 | 137 | ±2.3 | 156–119 |
| Cardiac index, L./min./M.$^2$ | 3.46 | ± .19 | 5.01–2.03 | 3.42 | ± .19 | 5.19–2.02 |
| A-V difference, volume per cent | 4.3 | ± .23 | 6.8–3.0 | 4.3 | ± .26 | 7.0–2.8 |
| Pulse rate, beat/min | 77 | ± .35 | 117–54 | 76 | ± .35 | 117–52 |

Average time between two successive determinations = 27 minutes (range 11 to 60).
Average time between beginning of study and second determination = 148 minutes (range 48 to 186).

It can be seen from Table I that the mean values of oxygen consumption, cardiac index, oxygen arteriovenous difference and pulse rate are almost identical in the first and second determinations. The correlation coefficient between the two successive determinations of oxygen consumption and two successive measurements of cardiac index are very high, respectively, $r = .734$ and $r = .999$ ($p$ for both $<0.0004$). Further statistical analysis indicates that there is no significant correlation between the variation in oxygen consumption and either the time between the beginning of the study and the second determination or the total time separating both determinations. Therefore the factor of time as a variant may, within the given limits, be neglected. Since it is necessary to expedite the procedure in cardiacs, only one control determination of cardiac output was made in all but one patient in this series. The analysis of differences presented in Table II gives the mean difference and the range of variation to be expected when a second determination is made within approximately thirty minutes of the first. It can be concluded therefore that if the oxygen consumption following injection of the drug does not vary from the control value by more than −18 to +12 cc. any cardiac output change greater than 9 per cent of the control measurement is due to the action of the drug.

TABLE II

ANALYSIS OF DIFFERENCES BETWEEN TWO SUCCESSIVE MEASUREMENTS OF CARDIAC OUTPUT IN TWENTY CONTROL PATIENTS NOT RECEIVING MEDICATION

| | Mean Difference | Range |
|---|---|---|
| Cardiac output in per cent of first determination | 4.8 | −9.0 to +9.2 |
| Oxygen consumption in cc./min./M.$^2$ body surface | 7.0 | −18 to +12 |
| Arteriovenous difference in volume per cent | 0.2 | −0.3 to +0.5 |
| Heart rate in beats per minute | 2.0 | −6 to +4 |

The range within which blood pressure measurements varied during the catheterization procedure is presented in Table III. To obtain these data an analysis was made of the control periods of twenty-three cardiac patients who subsequently received digoxin and in whom pulmonary artery, right ventricular and peripheral arterial pressures were repeatedly measured. The period of control observation aver-

aged thirty-two minutes, and the number of observations averaged three per patient. From this table it is evident that variations in pressures as measured by this technic are minimal in the right heart and somewhat larger in the peripheral artery.

TABLE III

ANALYSIS OF DIFFERENCES BETWEEN REPEATED CONTROL MEASUREMENTS OF BLOOD PRESSURES IN A GROUP OF TWENTY-THREE CARDIAC PATIENTS

| | Mean Difference | Range |
|---|---|---|
| Arterial blood pressures in mm. Hg | | |
| Systolic | 11.1 | −16 to +29 |
| Diastolic | 5.8 | −6 to +13 |
| Mean | 9.3 | −12 to +18 |
| Pulmonary arterial pressures in mm. Hg | | |
| Systolic | 1.9 | −4 to +5 |
| Diastolic | 1.5 | −4 to +1 |
| Mean | 1.9 | −5 to +5 |
| Right ventricular end diastolic pressure in mm. Hg | 1.4 | −2 to +4 |

Average time duration of control period = thirty-two minutes.

Average number of determinations in each patient = three.

The range of variation in these control studies (Tables II and III) is considerably less than in those previously published.[1] This difference may be partially accounted for by an increased experience in use of the technic in cardiac patients and also by the fact that during the period of observation no other procedure intervened between the measurements. In the previously reported "control" series positive pressure breathing was given between measurements.

The stable state of the patient in these studies, as indicated by the aforementioned data, considerably adds to the validity of the changes observed following drug administration.

The upper limit of normal pressure values used in this laboratory are as follows: Pulmonary artery and right ventricular systolic pressure = 30 mm. Hg, pulmonary artery diastolic pressure = 10 mm. Hg, pulmonary artery mean pressure = 15 mm. Hg, right ventricular end diastolic pressure = 5.0 mm. Hg. The range of variation in cardiac output among normal subjects, in L./min./sq. m. body surface area is between 2.70 and 3.50.

## RESULTS

The first three patients listed in Tables IV and VIIA had marked systemic hypertension and clinical manifestations of simple left ventricular failure. Clinically and physiologically the first patient (P. A.) showed the least degree of failure while the other two had signs of more advanced hypertensive disease. The control pulmonary artery systolic, diastolic and mean pressures of all were elevated. (Table IV.) The end diastolic pressure of the right ventricle however was normal, indicating a normal right auricular and peripheral venous pressure. The cardiac output was normal in one patient (P. A.), low normal in a second (J. B.) and reduced in the third (G. R.). Peripheral resistance was increased in all three patients, and the total and plasma blood volumes slightly increased in all three.

After administration of digoxin all three patients had a marked decrease in the lesser circulation hypertension. It is noteworthy that the end diastolic pressure in the right ventricle did not change. In each of these three patients the cardiac output rose 36 per cent, 22 per cent and 77 per cent, respectively, and the stroke volume increased markedly, 26 per cent, 53 per cent and 128, respectively. There was no consistent change in arterial blood pressures, one patient (P. A.) showing no change, the second (J. B.) a rise in systolic and mean pressures and a third (G. R.) a rise in systolic with a fall in diastolic and no change in the mean pressure. The peripheral resistance was reduced in all three patients. One patient (P. A.) showed no change in rate, a second patient (J. B.) a minimal slowing and the third patient (G. R.) showed a moderate slowing of the heart rate. Figure 1, showing the effect of digoxin in the patient, J. B., is illustrative of all three cases.

A fourth patient (T. B.), Tables IV, VIIA and Figure 2, had both hypertensive and arteriosclerotic heart disease and an old myocardial infarct. He presented the clinical picture of the previous three patients

and, in addition to the lesser circulation hypertension, had a very low cardiac output and stroke volume and a greater increase in total blood volume than the previous patients. Following digoxin this patient also exhibited a fall in the pulmonary pressures

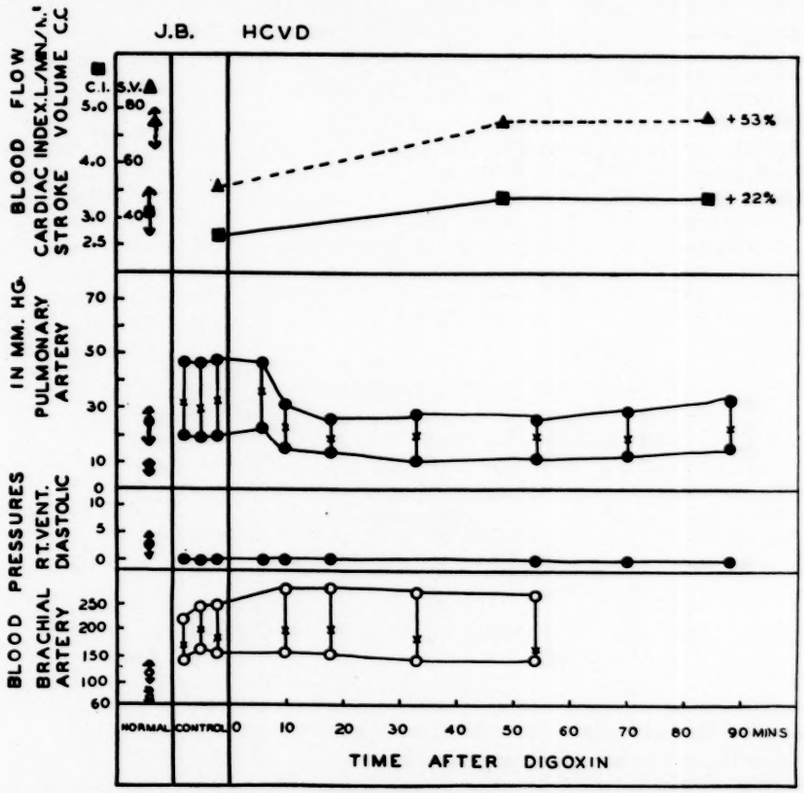


FIG. 1. The effect of intravenous digoxin in a case of left ventricular failure. Closed triangles = stroke volume; closed squares = cardiac index; closed circles = pulmonary artery systolic and diastolic, and right ventricular end diastolic pressures; open circles = brachial artery systolic and diastolic pressures; cross marks = mean pressures. The normal mean values and approximate range of variation are plotted in the first vertical column. Note (1) the increase in stroke volume and cardiac output accompanied by a fall to normal of the elevated pulmonary artery pressures, following administration of the drug, (2) the absence of change in the right ventricular end diastolic pressure and (3) the brachial artery pulse pressure increase.

from hypertensive to normal levels but responded with a smaller increase in cardiac output (12 per cent) and stroke volume (32 per cent). There was no change in arterial blood pressure, peripheral resistance or heart rate. Again the end diastolic pressure in the right ventricle was unaltered.

The fifth patient (R. M.), Tables IV, VIIA and Figure 3, with rheumatic heart disease, mitral stenosis and insufficiency and aortic insufficiency, had a very low cardiac output and stroke volume. It must be emphasized that with aortic insufficiency this stroke volume is merely an estimation, and the regurgitation *per se* probably plays a role in lowering the effective cardiac output. The typical pressure abnormalities of pure left-sided failure were noted. The blood volume was normal and peripheral resistance increased. After digoxin there was a marked increase in cardiac output and stroke volume (47 per cent and 83 per cent, respectively) and a fall to normal of the elevated pulmonary artery pressures. There was no change in right ventricular end diastolic pressure or in arterial blood pressures. There was a fall in peripheral resistance and the heart rate was definitely slowed.

TABLE IV

EFFECT OF INTRAVENOUS DIGOXIN ON BLOOD PRESSURES, CARDIAC OUTPUT, STROKE VOLUME AND HEART RATE IN FIVE PATIENTS WITH LEFT-SIDED HEART FAILURE

| Case | Time (min.) | Brachial Artery (mm. Hg) s/d | m | Pulmonary Artery (mm. Hg) s/d | m | Right Ventricle (mm. Hg) s/d | Cardiac Output (L./min.) | Stroke Volume (cc.) | Heart Rate (Beats min.) |
|---|---|---|---|---|---|---|---|---|---|
| P. A., male, fifty-eight years old; B.S.A. 1.91; HCVD, EH, NSR, PND, IIIC | Control | 200/100 | 144 | ..... | .. | ..... | .... | ... | 75 |
| | | 210/99 | 145 | 36/16 | 28 | ..... | .... | ... | 83 |
| | | 194/94 | 132 | 34/12 | 25 | ..... | 6.78 | 87 | 78 |
| | | 199/99 | 140 | 33/12 | 24 | 33/5 | 6.82 | 88 | 78 |
| | 7* | 204/101 | 142 | 32/11 | 24 | ..... | .... | ... | 75 |
| | 13 | ..... | ... | ..... | .. | ..... | 8.56 | 110 | 78 |
| | 14 | 212/98 | 141 | 26/12 | 19 | ..... | .... | ... | 78 |
| | 27 | 212/97 | 142 | 30/11 | 22 | 28/5 | .... | ... | 75 |
| | 36 | 202/90 | 133 | 29/9 | 21 | 28/5 | .... | ... | 77 |
| | 48 | 206/90 | 133 | 28/9 | 20 | ..... | .... | ... | 68 |
| | 58 | 214/94 | 138 | 26/9 | 18 | | | | |
| | 63 | ..... | ... | ..... | .. | ..... | 8.24 | 110 | 75 |
| | 67 | 210/92 | 137 | 25/8 | 17 | ..... | .... | ... | 75 |
| | 85 | 217/99 | 139 | 25/11 | 17 | 26/6 | .... | ... | 75 |
| J. B., male, thirty-one years old; B.S.A. 2.0; HCVD, EH, NSR gallop, PND, IVD, arteriolar nephrosclerosis with uremia and anemia; hypertensive retinopathy and encephalopathy | Control | 219/146 | 172 | 47/20 | 32 | 47/−3 | .... | ... | 100 |
| | | 244/156 | 189 | 47/19 | 30 | 47/−2 | .... | ... | 100 |
| | | 247/148 | 185 | 48/20 | 33 | 48/−1 | 5.59 | 53 | 104 |
| | 6* | ..... | ... | 47/23 | 36 | 47/−2 | .... | ... | 93 |
| | 10 | 276/159 | 199 | 32/15 | 23 | 30/0 | .... | ... | 88 |
| | 18 | 278/154 | 201 | 26/12 | 19 | 28/0 | .... | ... | 88 |
| | 33 | 268/145 | 183 | 28/11 | 20 | ..... | .... | ... | 88 |
| | 48 | ..... | ... | ..... | .. | ..... | 6.76 | 77 | 88 |
| | 54 | 265/144 | 162 | 26/12 | 20 | 26/−1 | .... | ... | 88 |
| | 70 | ..... | ... | 29/13 | 19 | 30/0 | .... | ... | 86 |
| | 84 | ..... | ... | ..... | .. | ..... | 6.83 | 79 | 86 |
| | 88 | ..... | ... | 33/16 | 23 | 30/0 | .... | ... | 86 |
| | 95 | ..... | 164 | ..... | .. | 28/−2 | .... | ... | 93 |
| G. R., male, fifty-four years old; B.S.A. 1.78; HCVD, EH, NST gallop, PND, IVD, hypertensive retinopathy | Control | 197/128 | 152 | 60/43 | 48 | 60/3 | .... | ... | 120 |
| | | 215/144 | 166 | ..... | 50 | ..... | 3.92 | 33 | 120 |
| | | 203/138 | 158 | ..... | 53 | ..... | .... | ... | 120 |
| | 23* | ..... | ... | ..... | .. | ..... | 5.35 | 54 | 100 |
| | 28 | 224/115 | 155 | 48/16 | 30 | 48/3 | .... | ... | 100 |
| | 38 | 221/115 | 153 | 44/15 | 25 | 44/2 | .... | ... | 100 |
| | 70 | 202/100 | 138 | 37/13 | 21 | 37/2 | .... | ... | 93 |
| | 78 | ..... | ... | ..... | .. | ..... | 6.95 | 75 | 93 |
| T. B., male, fifty-nine years old; B.S.A. 1.93; HCVD, ASHD, EH, CS, MF, old infarct, NSR, LBBB, gallop, PND, angina, IIIC | Control | 148/85 | 106 | 40/22 | 26 | 40/1 | 4.10 | 53 | 78 |
| | | 137/80 | 102 | 40/20 | 26 | ..... | .... | ... | 78 |
| | 9* | 149/85 | 107 | 33/17 | 21 | ..... | .... | ... | 71 |
| | 14 | 146/80 | 102 | 30/14 | 18 | 30/2 | .... | ... | 65 |
| | 20 | ..... | ... | ..... | .. | ..... | 4.55 | 70 | 65 |
| | 25 | 151/83 | 105 | 29/17 | 21 | ..... | .... | ... | 65 |
| | 30 | 144/78 | 99 | 27/10 | 15 | 27/2 | .... | ... | 65 |
| | 35 | ..... | ... | ..... | .. | ..... | 4.39 | 68 | 65 |
| | 42 | 154/86 | 103 | 25/13 | 17 | 25/1 | .... | ... | 68 |
| | 52 | 140/79 | 96 | 23/11 | 15 | 23/1 | .... | ... | 71 |
| | 69 | 146/82 | 101 | 24/11 | 15 | 24/2 | .... | ... | 65 |

TABLE IV (*Continued*)

| Case | Time (min.) | Brachial Artery (mm. Hg) s/d | Brachial Artery (mm. Hg) m | Pulmonary Artery (mm. Hg) s/d | Pulmonary Artery (mm. Hg) m | Right Ventricle (mm. Hg) s/d | Cardiac Output (L./min.) | Stroke Volume (cc.) | Heart Rate (Beats min.) |
|---|---|---|---|---|---|---|---|---|---|
| R. M., male, forty-nine years old; B.S.A. 1.33; RHD, EH, MS, MI, AI, NSR, LBBB, gallop, PND, IIIC | Control | 144/60 | 100 | 56/31 | 39 | 56/3 | 2.13 | 23 | 94 |
| | 6† | 143/50 | 93 | 49/19 | 30 | 49/0 | .... | ... | 78 |
| | 18 | 154/51 | 98 | 28/10 | 17 | 28/0 | .... | ... | 75 |
| | 27 | 150/47 | 94 | 20/7 | 9 | 20/0 | .... | ... | 75 |
| | 33 | ..... | ... | ..... | .. | ..... | 2.98 | 40 | 75 |
| | 38 | 162/52 | 100 | 20/9 | 13 | 20/0 | .... | ... | 75 |
| | 47 | 153/48 | 93 | 18/6 | 9 | 18/0 | .... | ... | 75 |
| | 54 | ..... | ... | ..... | .. | ..... | 3.13 | 42 | 75 |
| | 60 | 156/48 | 94 | 19/8 | 11 | 19/0 | .... | ... | 75 |

* Time after start of injection of 1.5 mg. digoxin.
† Time after start of injection of 1.0 mg. digoxin.
*s* = systolic. *d* = diastolic. *m* = mean.
B.S.A. = Body surface area in square meters.
ASHD = Arteriosclerotic heart disease.
HCVD = Hypertensive cardiovascular disease.
RHD = Rheumatic heart disease.
AI = Aortic insufficiency.
CS = Coronary sclerosis.
EH = Enlarged heart.
MI = Mitral insufficiency.
MF = Myocardial fibrosis.
MS = Mitral stenosis.
PND = Paroxysmal nocturnal dyspnea.
NSR = Normal sinus rhythm.
LBBB = Left bundle branch block

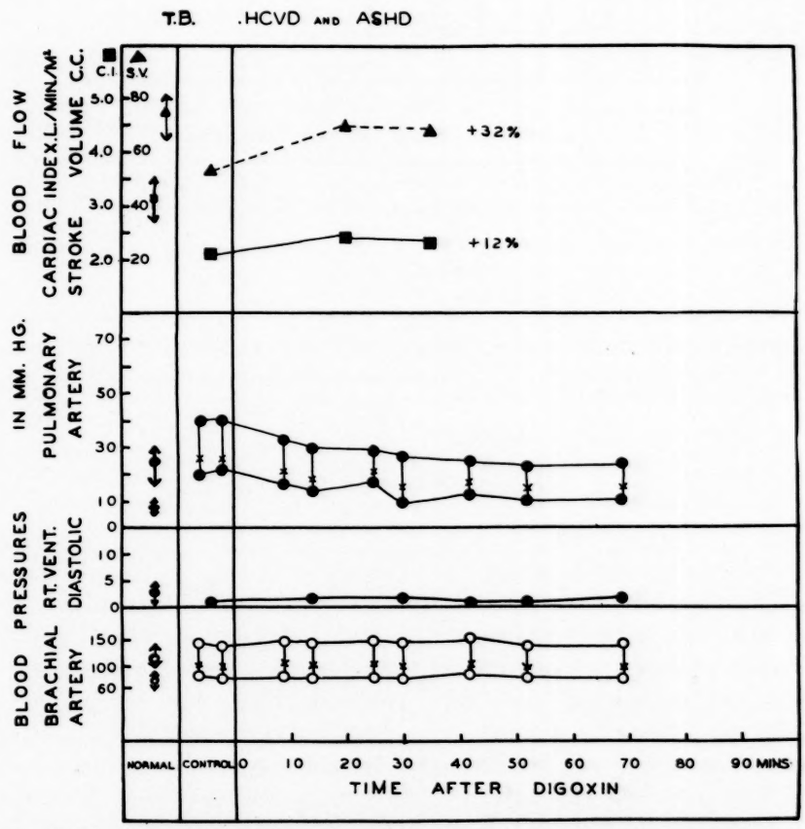


FIG. 2. The effect of digoxin in left ventricular failure. (For symbols see Figure 1.) Note (1) the initially low cardiac output, (2) the smaller increase in cardiac output as compared to the other cases, (3) marked pressure drop in the pulmonary artery, (4) no change in right ventricular end diastolic pressure and (5) insignificant changes in brachial artery pulse pressure.

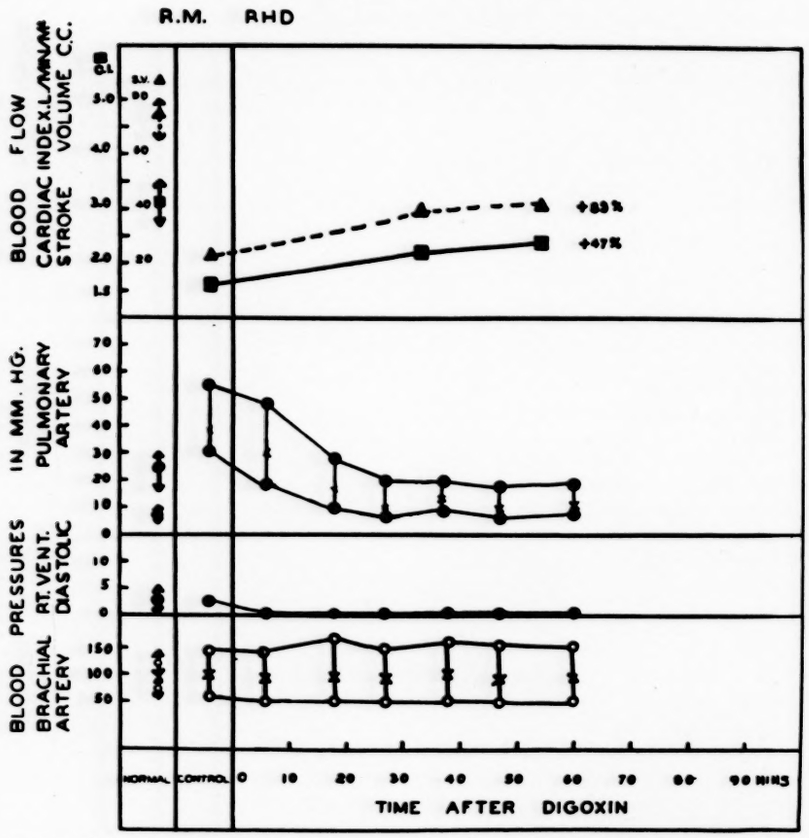


FIG. 3. The effect of digoxin in left ventricular failure. (For symbols see Figure 1.) The hemodynamic response is identical with that in the previous cases (Figs. 1 and 2).

TABLE V

EFFECT OF QUINIDINE SULFATE ON BLOOD PRESSURES, CARDIAC OUTPUT, STROKE VOLUME AND HEART RATE IN A FULLY DIGITALIZED PATIENT WITH RHEUMATIC HEART DISEASE AND LFFT-SIDED FAILURE

| Case | Time (min.) | Brachial Artery (mm. Hg) *s/d* | *m* | Pulmonary Artery (mm. Hg) *s/d* | *m* | Right Ventricle (mm. Hg) *s/d* | Cardiac Output (L./min.) | Stroke Volume (cc.) | Heart Rate (Beats min.) |
|---|---|---|---|---|---|---|---|---|---|
| J. L., male, sixty-three years old; B.S.A. 1.43; RHD, EH, MS, MI, AI, NSR, IIIC | Control | 147/77 | 106 | 40/14 | 23 | 40/2 | 2.93 | 43 | 68 |
| | | 150/79 | 109 | ..... | .. | .... | .... | .. | 68 |
| | 29* | 134/70 | 97 | ..... | .. | .... | .... | .. | 75 |
| | 54 | 109/56 | 73 | ..... | .. | .... | .... | .. | 75 |
| | 62 | 101/55 | 74 | 30/7 | 15 | .... | .... | .. | 75 |
| | 77 | ..... | ... | ..... | .. | .... | 4.02 | 54 | 75 |
| | 92 | 99/53 | 72 | 31/9 | 16 | .... | .... | .. | 75 |
| | 97 | 102/56 | 75 | ..... | .. | 26/0 | .... | .. | 75 |
| | 117 | ..... | ... | ..... | .. | .... | 3.50 | 47 | 75 |
| | 132 | 109/59 | 82 | ..... | .. | 25/2 | .... | .. | 75 |

* Time after 0.8 Gm. quinidine sulfate by mouth.
*s* = systolic. *d* = diastolic. *m* = mean.
RHD = Rheumatic heart disease.
AI = Aortic insufficiency.
EH = Enlarged heart.
MI = Mitral insufficiency.
MS = Mitral stenosis.
NSR = Normal sinus rhythm.

In summary, these five patients with left-sided heart failure responded to digoxin in exactly the same manner; without change in right heart end diastolic pressure the cardiac output and stroke volume rose and the pulmonary hypertension was diminished. The apical diastolic gallop found in four patients disappeared after digoxin. In two patients the heart rate fell significantly. The peripheral resistance was decreased in four.

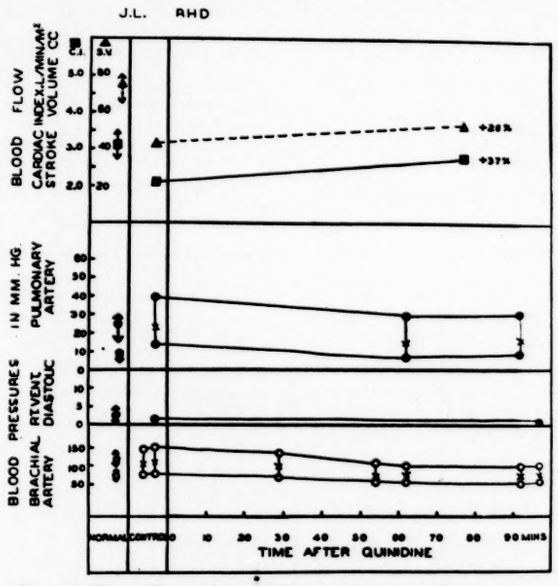


FIG. 4. The effect of quinidine sulfate in left ventricular failure. (For symbols see Figure 1.) Note that following a decrease in peripheral resistance induced by quinidine, there was (1) a rise in stroke volume and cardiac output, (2) a fall in pulmonary artery pressures and (3) no change in right ventricular end diastolic pressure.

The data in a patient with left-sided heart failure who received quinidine is presented in Tables V, VIIB and Figure 4. This patient with rheumatic heart disease was digitalized and symptom-free on bed rest but nevertheless had pulmonary hypertension and a low cardiac output and stroke volume. There was a normal end diastolic pressure in the right ventricle, a normal blood volume and increased peripheral resistance. Quinidine, 0.8 Gm. orally, produced a marked fall in arterial blood pressure, a fall in peripheral resistance and a rise of 37 per cent in cardiac output and 26 per cent in stroke volume, with a return to normal of the elevated pulmonary artery pressures. The heart rate did not vary significantly.

In contrast to these patients is a patient with chronic cor pulmonale in congestive failure who was also treated with digoxin.

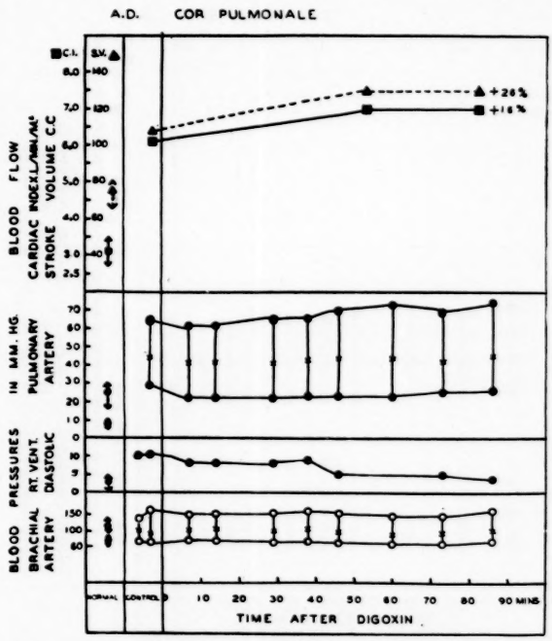


FIG. 5. The effect of digoxin in right heart failure due to cor pulmonale. (For symbols see Figure 1.) Note that (1) the initially elevated cardiac output rose considerably after digoxin, (2) the elevated right ventricular end diastolic pressure returned to normal and (3) with the increase in stroke volume the pulmonary artery systolic pressure rose, a response different from the pulmonary artery response in patients in left ventricular failure.

(Tables VI, VIIC and Fig. 5.) The elevated pulmonary artery pressures were accompanied by an elevated end diastolic pressure in the right ventricle as would be expected in congestive right-sided heart failure. Clinically the patient had an enlarged liver and peripheral edema. The elevated cardiac output, polycythemia with increased total blood and plasma volumes and arterial blood oxygen unsaturation complete the classical picture of cor pulmonale in cardiac failure.

Following injection of 1.5 mg. of digoxin there was an increase of 16 per cent in cardiac output and of 26 per cent in stroke volume. (Tables VI and VIIC.) The response of the pulmonary circulation to this rise in

output was in sharp contrast to that demonstrated by the patients with left heart failure. The elevated right ventricular end diastolic pressure returned to normal with the increase in stroke volume. The pulmonary artery and right ventricular systolic pressures, however, showed an increase after digoxin. The systolic pressure in the pulmonary artery and right ventricle rose from 63 to 74 mm. Hg without any striking change in pulmonary artery diastolic or mean pressures. Changes were minimal in peripheral resistance and arterial pressures. The heart rate slowed slightly.

TABLE VI

EFFECT OF DIGOXIN ON BLOOD PRESSURES, CARDIAC OUTPUT, STROKE VOLUME AND HEART RATE IN A PATIENT WITH COR PULMONALE AND CONGESTIVE HEART FAILURE

| Case | Time (min.) | Brachial Artery (mm. Hg) *s/d* | *m* | Pulmonary Artery (mm. Hg) *s/d* | *m* | Right Ventricle (mm. Hg) *s/d* | Cardiac Output (L./min.) | Stroke Volume (cc.) | Heart Rate (Beats min.) |
|---|---|---|---|---|---|---|---|---|---|
| A. D., female, fifty-five years old; B.S.A. 1.65; cor pulmonale. EH, NSR, chronic bronchial asthma; mild emphysema | Control | 140/75 | 103 | 63/29 | 44 | 63/10 | .... | ... | 97 |
| | | 160/71 | 95 | ..... | .. | 62/11 | 10.0 | 103 | 97 |
| | 7* | 147/77 | 106 | 62/22 | 41 | 62/8 | .... | ... | 88 |
| | 14 | 150/74 | 107 | 62/22 | 41 | 62/8 | .... | ... | 85 |
| | 29 | 152/72 | 104 | 65/22 | 41 | 65/8 | .... | ... | 88 |
| | 38 | 161/74 | 110 | 66/23 | 43 | 66/9 | .... | ... | 88 |
| | 46 | 152/71 | 102 | 69/23 | 44 | 69/5 | .... | ... | 88 |
| | 53 | ..... | ... | ..... | .. | ..... | 11.6 | 130 | 88 |
| | 60 | 144/68 | 96 | 73/23 | 44 | ..... | .... | ... | 88 |
| | 73 | 145/67 | 99 | 69/25 | 42 | 69/5 | .... | ... | 88 |
| | 82 | ..... | ... | ..... | .. | ..... | 11.6 | 130 | 88 |
| | 86 | 159/75 | 108 | 74/26 | 45 | 74/4 | .... | ... | 88 |

* Time after start of injection of 1.5 mg. digoxin.
*s* = systolic. *d* = diastolic. *m* = mean.
EH = Enlarged heart.
NSR = Normal sinus rhythm.

## COMMENTS

The feature held to be characteristic of left heart failure is pulmonary congestion. In order to evaluate the various mechanisms concerned in the production of such congestion a comment on the known characteristics of pulmonary circulation in man becomes necessary.

The pulmonary vascular system is characterized by low resistance because of easy deformability and, therefore, increased distensibility. Measurement of pressures and flow indicates that in the normal pulmonary circulation the resistance at rest is about one-tenth the resistance in the systemic circulation. Furthermore, the deformability of the pulmonary system is such that it can accommodate a three-fold cardiac output increase without pressure changes in the pulmonary artery.[5,6]

In any discussion of the pulmonary vascular system not only its inherent characteristics must be considered but also the influence of left auricular pressure variations must be evaluated. There are anatomic and physiologic differences between the two sides of the heart. As Cournand[7] originally commented, "There are differences between (a) the two auricles, the left auricular wall being thicker than the right; (b) their venous reservoir, the four pulmonary veins being shorter and their diameter smaller than the superior or inferior vena cava; and (c) both ventricles, the muscular development of the left ventricle being much greater than the right. These anatomic differences suggest that the left auricle is less deformable than the right, that its venous reservoir has a smaller capacity, and finally that effects of muscular activity of the left ventricle upon volume and tension in the left auricle may be more pronounced than similar activity of the right ventricle

TABLE VII

PHYSIOLOGIC DATA CONCERNING CARDIAC OUTPUT AND BLOOD VOLUME IN (1) FIVE PATIENTS WITH LEFT-SIDED HEART FAILURE TREATED WITH DIGOXIN, (2) ONE PATIENT WITH LEFT-SIDED FAILURE TREATED WITH QUINIDINE AND (3) ONE PATIENT WITH COR PULMONALE TREATED WITH DIGOXIN

| Case | Time (min.) | Cardiac Index (L./min./M.² BSA) | Oxygen Consumption (cc./min./M.² BSA) | AV Oxygen Difference (vol. %) | Arterial | | | Peripheral Resistance (dynes sec. cm.⁻⁵) | Blood Volume§ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Blood Content (vol. %) | Oxygen Capacity (vol. %) | Saturation (%) | | TBV** (cc./M.² BSA) | PV†† | Hematocrit (%) |
| | | | | | (1) | | | | | | |
| P. A. | Control | 3.55 | 160 | 4.5 | 16.3 | .... | .... | 1555 | 2870 | 1810 | 37 |
| | | 3.63 | 160 | 4.4 | 16.2 | 16.6 | 97.5 | 1600 | | | |
| | 13* | 4.47 | 161 | 3.6 | 15.4 | 16.2 | 96.0 | 1315 | | | |
| | 63 | 4.45 | 160 | 3.6 | 15.4 | 16.4 | 96.0 | 1330 | | | |
| J. B. | Control | 2.77 | 177 | 6.4 | 12.5 | 14.8 | 86.0 | 2650 | 3085 | 2063 | 33 |
| | 48* | 3.35 | 164 | 4.9 | 11.9 | 13.6 | 89.0 | 1915 | | | |
| | 84 | 3.38 | 162 | 4.8 | 11.6 | 13.3 | 89.0 | 1920 | | | |
| G. R. | Control | 2.20 | 154 | 7.0 | 16.7 | 17.6 | 95.0 | 3490 | 3138 | 1740 | 45 |
| | 23* | 3.00 | 154 | 5.2 | 16.6 | .... | .... | 2555 | | | |
| | 78 | 3.91 | 152 | 3.9 | 15.9 | .... | .... | 1590 | | | |
| T. B. | Control | 2.14 | 147 | 6.9 | 19.9 | 20.6 | 97.5 | 2020 | 3680 | 1928 | 48 |
| | 20* | 2.37 | 142 | 6.0 | 18.7 | 20.6 | 91.6 | 1840 | | | |
| | 35 | 2.29 | 128 | 5.6 | 18.6 | .... | .. | 1880 | | | |
| R. M. | Control | 1.60 | 155 | 9.7 | 17.5 | 19.1 | 93.0 | 3760 | 2670 | 1465 | 45 |
| | 33† | 2.23 | 156 | 7.0 | 17.0 | 17.9 | 96.0 | 2780 | | | |
| | 54 | 2.35 | 160 | 6.8 | 16.7 | .... | .... | 2400 | | | |
| | | | | | (2) | | | | | | |
| J. L. | Control | 2.05 | 121 | 5.9 | 18.8 | 19.8 | 95.9 | 2980 | 2790 | 1500 | 45 |
| | 77‡ | 2.81 | 127 | 4.5 | 18.3 | 19.7 | 93.8 | 1500 | | | |
| | 117 | 2.45 | 127 | 5.2 | 18.1 | 19.0 | 96.0 | 1875 | | | |
| | | | | | (3) | | | | | | |
| A. D. | Control | 6.06 | 170 | 2.8 | 12.3 | 20.5 | 60.0 | 720 | 6060 | 2043 | 66 |
| | 53* | 7.05 | 176 | 2.5 | 11.1 | 20.4 | 65.0 | 625 | | | |
| | 82 | 7.04 | 162 | 2.3 | 12.3 | 20.3 | 61.0 | 725 | | | |

* Time after start of injection of 1.5 mg. digoxin.
† Time after start of injection of 1.0 mg. digoxin.
‡ Time after 0.8 Gm. quinidine sulfate by mouth.
** TBV = Total blood volume.
†† PV = Plasma volume.

§ Predicted Values:

| | Total Blood | Plasma | Hematocrit |
|---|---|---|---|
| Male | 2900 | 1600 | 45 |
| Female | 2670 | 1600 | 40 |

upon volume and tension in the right auricle." There is increasing evidence that mean pressure in the left auricle is normally higher than in the right auricle and that the distensibility of the left ventricle, left auricle and pulmonary veins is less than it is in similar structures of the right heart. This evidence stems from direct measurements of left auricular pressure curves in man,[7] and a similar conclusion is reached from the indirect measurements reported by Dexter[8] and Werkö.[9] The characteristic difference between the two auricles has recently been confirmed in dogs by Opdyke et al.[10]

It follows from these studies that for the same volume change there will be a greater pressure change in the left heart and pulmonary veins than would be found in the right heart and systemic veins during any one cardiac cycle. This in turn probably favors the onset of pulmonary congestion earlier than systemic congestion for a comparable increase in residual volume of the two ventricles. Furthermore, the mean pressure difference between the pulmonary artery and the left auricle in normal subjects is very small, probably less than 10 mm. Hg. As the arterioles and precapillaries have very little smooth muscle most of the pressure drop must be between the main pulmonary artery and its branches. Conversely, with resistance in pulmonary arterioles unchanged any increase in pressure in the pulmonary veins must easily raise the pressure in the capillaries, precapillaries and arterioles and eventually effect a rise in the mean pulmonary arterial pressure.

Failure of the left heart results in an increase in the residual blood volume in the left ventricle and auricle and hence produces an increase in pressure in the latter chamber which is easily reflected throughout the pulmonary vascular tree producing pulmonary hypertension. Clinically this is expressed as pulmonary congestion.

It is quite obvious that pulmonary hypertension may also be a manifestation of abnormalities of the pulmonary vascular bed resulting from a diminution in capacity of the arteriolar and capillary system.

The five patients treated with digoxin clinically had evidence of left-sided failure. In four of these patients failure of the left ventricle to empty adequately resulted in an increase in residual blood in the left ventricle with a subsequent increase in filling pressure. In one patient (R. M.) the mitral stenosis itself might have produced elevation of the pressure in the left auricle for mechanical reasons. However, aortic insufficiency could have been the cause of left ventricular failure and of the rise in left auricular pressure.

In all these patients an increased stroke volume occurred concomitantly with a reduction in the pulmonary hypertension following digoxin administration. This suggests a more adequate emptying of the left ventricle and a reduction in the residual blood volume of this chamber and left auricle. The increased systemic flow obviously results in an increased return of blood to the right heart. This was accomplished, however, without detectable change in the end diastolic pressure of the right ventricle. This is the characteristic response of a normally functioning right heart in which large volume changes are associated with minimal filling pressure increase.[10,11] Since the pulmonary pressures of the patient with rheumatic heart disease, mitral stenosis and aortic insufficiency (R. M.) fell to normal after administration of digoxin, it is difficult to escape the conclusion that his pulmonary hypertension was the result of failure of the left ventricle to empty adequately rather than the result of mechanical obstruction at the mitral valve.

In the patient (J. L.) treated with quinidine, who also had mitral stenosis and aortic insufficiency, the pulmonary artery pressures also returned to normal levels. This suggests that left ventricular failure rather than mechanical obstruction at the mitral valve produced pulmonary hypertension. With the peripheral vasodilatation produced by quinidine the left ventricle was

able to empty more completely, thus reducing the pressures in the lesser circulation. This is further evidence of the importance of the action of the left ventricle upon the pulmonary circulation.

An entirely different physiologic situation existed in the patient with chronic cor pulmonale and pulmonary hypertension. In this instance reduction in pulmonary arteriolar caliber was the underlying cause of hypertension of the lesser circulation as was suggested by extensive pulmonary function studies. The right heart, working against markedly increased resistance, was failing to empty itself as was evidenced by the increase in end diastolic pressure. The left heart, however, was presumably not failing to empty itself efficiently although the assumption of normal left auricular pressure cannot be proved.

After digoxin better emptying of the right ventricle reduced the residual volume and filling pressure but caused an increase in the pulmonary artery systolic pressure. This suggests that when an increase in blood flow takes place within a pulmonary vascular bed with a pathologically restricted capacity it cannot be accommodated without a rise in pressure in the pulmonary artery. A similar effect upon the pulmonary arterial pressure in patients with a restricted pulmonary vascular bed has been observed when cardiac output is increased following exercise.[5,6]

It should be emphasized that all the hemodynamic changes produced by the drugs here noted were only followed for a period of one and one-half to two hours. These acute changes do not necessarily reflect the final or optimal effect of the medication and any conclusions as to long term results are not justified.

*Mode of Action of Digoxin.* In recent attempts to delineate more precisely the mode of action of digitalis preparations in the human circulation a peripheral venous action has been postulated.[12] This assumption was based on material in which the right atrial mean pressure was used as an indication of the filling pressure of the right heart. Since in the present study there was no change after digoxin in the right ventricular end diastolic pressure, which reflects central venous pressures but is a better index of the filling pressure of the right heart than the mean auricular pressure, this assumption of a predominantly venous action of digoxin is not tenable in cases of left ventricular failure. The improvement in stroke volume and reduction in pulmonary congestion on the other hand suggest a predominantly myocardial effect of the drug. It would seem unreasonable to postulate instead a specific isolated effect of the drug on the pulmonary venous bed. With no change in heart rate in two of the five patients studied it is apparent that this myocardial action is, at least in some cases, independent of a change in the heart rate.

The action of digitalis bodies upon the peripheral arteriolar bed has also been much discussed and in man the effect upon systemic blood pressure has been reported as variable.[13–15] Analysis of changes in arterial blood pressure following intravenous digoxin in this group of patients contributes additional information to solution of this problem. As seen in Figure 6 the five patients with left ventricular failure showed either a small fall or no change in mean arterial pressure as the cardiac output rose in varying degrees. These changes indicate a moderate reduction in peripheral resistance. They are in sharp contrast to the effect of a similar dose of the drug in two subjects with normal hearts[16] plotted on the same graph. In the latter cases a fall in cardiac output was accompanied by no change in arterial mean pressure in one subject and a marked rise in the other, indicating in both cases an increase in peripheral resistance. A similar response has been observed in a larger group of cardiac patients with enlarged hearts but no evidence of failure.[16] This vasoconstrictor effect has also been observed in animals given large doses of digitalis.[13–14]

In the group of patients with left ventricular failure it is unlikely that a primary vasodilator effect alone could account for

the increase in cardiac output. This is made evident by a comparison of blood pressure changes in those given digoxin with those seen in three patients with cardiac failure treated with quinidine, a drug known to produce vasodilatation.[1,17] As can be seen

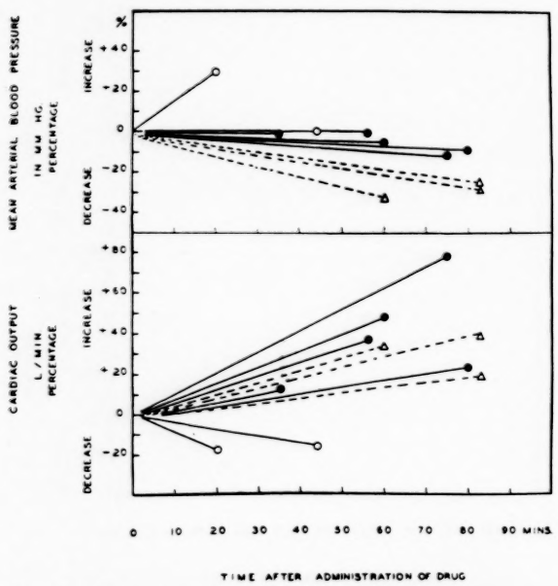


FIG. 6. Simultaneous brachial artery mean blood pressures and cardiac output changes following digoxin and quinidine. Open circles = patients with normal circulation receiving intravenous digoxin; closed circles = patients in left ventricular failure receiving intravenous digoxin; open triangles = patients in cardiac failure receiving 0.8 Gm. quinidine sulfate.

in Figure 6 the mean arterial pressure fall was much greater in the patients given quinidine for an increase in cardiac output which was usually smaller than in the patients given digoxin.

All these data suggest that the changes in peripheral vascular resistance after digoxin represent reflex alterations in dynamics secondary to the increase in stroke volume rather than a primary effect upon the arterioles. This homeostatic response could be mediated through the moderator nerves (aortic body and carotid sinus) or through effects upon the central vasomotor center. One cannot rule out an accompanying vasoconstrictor effect in these cardiac patients but if this antagonistic effect is present it must have been overcome by reflex vasodilatation.

## SUMMARY AND CONCLUSIONS

1. The early effect of intravenous digoxin is studied by the cardiac catheterization procedure in five patients with left-sided heart failure.

2. Digoxin produced a significant rise in cardiac output and stroke volume accompanied by a decrease in pulmonary arterial pressure in each of these five patients. These changes were effected without alteration in the right ventricle end diastolic pressure and therefore cannot be ascribed to an action of the drug upon the systemic venous system but rather are interpreted as an action of digoxin upon the myocardium.

3. Similar changes in cardiac output, stroke volume and pulmonary arterial pressure were observed in a patient with left ventricular failure after the peripheral resistance had been lowered by quinidine.

4. The tentative conclusion can therefore be reached that regardless of the cause of the stroke volume increase—myocardial action or a reduction in peripheral vascular resistance—the pulmonary congestion in six patients with left ventricular failure was relieved as a result of more satisfactory emptying of the left ventricle.

5. The conclusion that ventricular ejection and ventricular filling are mutually dependent upon the functional state of the myocardium seems inescapable.

6. As a contrast to the patients with left ventricular failure the effect of digoxin upon pulmonary blood flow and blood pressures in a patient with cor pulmonale is presented.

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# Coarctation of the Aorta*

## *Photo-electric Plethysmography and Direct Arterial Blood Pressure Measurement as an Aid in Diagnosis*

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THE clinical diagnosis of coarctation of the aorta can be made without difficulty when there is enough constriction of the aorta to cause collateral circulation to become well established. However, the degree of constriction may vary from a slight indentation to practically complete obliteration. The site of coarctation may also vary and anomalies of the great vessels may be present. Therefore, it is advantageous to establish the site and degree of the constriction in order to decide whether or not the condition can be corrected surgically and whether operation is likely to be hazardous.

The purpose of this report is to present the combination of two well established methods for the study of blood flow and blood pressure, namely, photo-electric plethysmography and direct measurements of arterial blood pressure as an aid to the diagnosis and location of coarctation of the aorta. By these means the relative blood flow of peripheral parts can be estimated and accurate blood pressure in an extremity can be measured.

### METHOD

Two photo-electric plethysmographs were used to compare simultaneously the relative blood flow in the ear lobes, fingers, scrotum or toes. The photo-electric plethysmograph consisted of a 2.2 volt pencil flashlight bulb as a light source and a photo-electric cell (Cetron 22-A. B.) in a small metal holder which could be adjusted to fit around a peripheral part. Variations in the density of the part were amplified and by means of a rapidly moving galvanometer (Sanborn cardiette) were recorded on a kymographic camera, the speed of which could be varied from 0.2 mm. per second to 75 mm. per second. Changes both in amplitude of pulse and opacity of the part were recorded semi-quantitatively. A Hamilton optical manometer recorded blood pressure simultaneously, as well as the contour of the pulse. Fourteen cases of coarctation of the aorta were studied; one patient (J. F.) had undergone surgical correction by an end-to-end anastomosis of the aorta; another (W. W.) was studied before and after operative correction of the defect. All measurements were made in the horizontal position and in a constant room temperature of 80°F.

### RESULTS

The systolic blood pressure in the femoral artery in normal subjects is approximately 20 mm. Hg higher than in the axillary, the diastolic being about the same when measured by direct arterial puncture.[1] Blood flow as indicated by the amplitude of the pulse wave is approximately the same or slightly less in the scrotum as compared with the ear lobe, or the toes as compared with the fingers. A comparison for absolute values between subjects cannot be made because of variations in the thickness of the peripheral parts.

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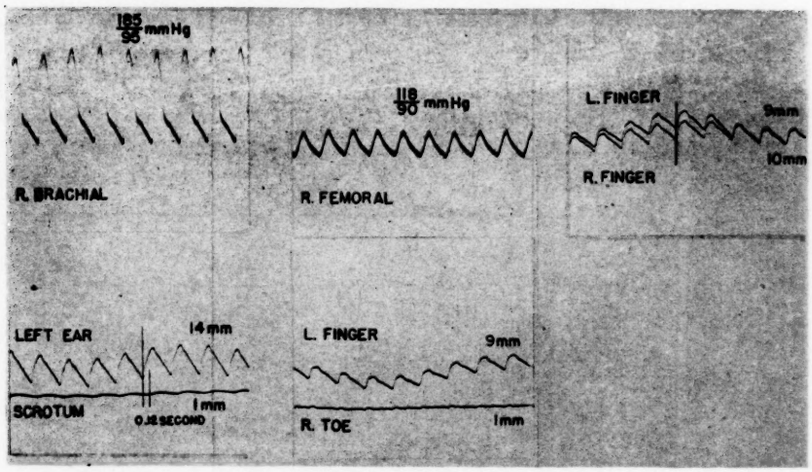


FIG. 1. Case IV, L. H. Photographic records of arterial pressure in the brachial and femoral arteries and of photoelectric plethysmograms in the fingers, toes, ear and scrotum. Note the change in contour of the femoral pulse. There is no difference in the timing of the pulses in the two fingers but a delay of 0.12 seconds between that in the ear and scrotum is evident. Note the abnormally small pulse in the toe. The camera speed was 25 mm. per second.

In a normal man the pulse wave velocity is 5 to 9 meters per second, depending upon the size and elasticity of the particular artery or group of arteries.[2] The velocity in the aorta is slower than that in peripheral vessels. The time lag between the rise of the pulse waves in the fingers and toes varies from 0.06 to 0.12 seconds. Since the distance between the finger and toe is about 40 per cent of the height, a rough estimate of the velocity of the pulse wave can be made. In four normal young adults this varied from 6.2 to 10 M. per second. The ear to scrotum velocity was much slower owing probably to the diameters and elasticity of the vessels traversed and to the special character of the tissues. (3.2 to 3.5 M. per second assuming a distance of about 20 per cent of the height.)

Comparing the above "normal" findings with those of severe, moderate and subclinical coarctation, striking differences were found. Figure 1 shows the results in a patient with severe coarctation (Case IV, Tables I and II.) The significant findings were: (1) a marked diminution in the systolic pressure in the femoral artery (118 mm. Hg) as compared to the brachial artery (185 mm. Hg) while the diastolic pressures were approximately the same; (2) marked diminution in the amplitude of the pulse wave of the scrotum (1 mm.) as compared to the left ear lobe (14 mm.), and of the toe (1 mm.) as compared to the finger (9 mm.); (3) delay of 0.12 seconds in the rise of the pulse wave of the scrotum as compared to the ear (pulse wave velocity 2.6 M. per second) and (4) equal pulsations in the fingers of the two hands. From these data one can conclude that the coarctation was distal to the origin of the left subclavian artery and was probably of the adult type. The marked diminution of the pulse amplitude in the scrotum and toes is compatible with a severe constriction of the aorta. These findings were in keeping with the clinical signs.

Figure 2 (Case III) represents a case of moderately severe coarctation, with aortic insufficiency probably on the basis of rheumatic heart disease. Photo-electric plethysmography revealed that the amplitude of the pulse of the left ear was 32 mm.; of the right, 7 mm.; of the index finger of the left hand, 31 mm.; of the right, 35 mm.; of the left index finger 32 mm.; of the right second toe, 3.5 mm., with a delay of approximately 0.12 seconds in the pulse wave of the toe. (Velocity 3.8 M. per second.) The amplitude in the left second toe was

9 mm. and in the right, 5 mm. The right brachial blood pressure was 214 mm. Hg systolic and 57 mm. diastolic; the left brachial was 124 mm. systolic and 70 diastolic and the right femoral artery was 87 mm. systolic and 54 diastolic.

because of the presence of hypertension, shortness of stature, hypo-ovarianism and an abnormally short fourth toe.[3] The blood pressure in the legs by the auscultatory method using the usual size cuff was found by several observers to be higher than it was

TABLE I

CLINICAL FINDINGS IN PATIENTS WITH COARCTATION OF THE AORTA

| Case No. | | Duration of Symptoms (mo.) | Age When Diagnosis Was Made | Symptoms and Signs | | | | | | | | | | | Pulsations | | | Evidence of Collateral Circulation | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex | Age | | | Dyspnea | Edema | Fatigue | Palpitation | Precordial Pain | Claudication | Headache | Hypogonadism | Short Stature | Abnormal Digits‡ | B.M.R. (Per Cent) | Femoral | Popliteal | Dorsalis Pedis | Intercostal Pulsation | Subscapular Pulsations | Deep Epigastric | Notching of Ribs in X-ray | Cardiac Enlargement from X-ray | Aortic Insufficiency | Systolic Murmur | Electrocardiographic Findings |
| I ♀ | 22 | 21 | 21 | + | 0 | + | 0 | 0 | 0 | 0 | + | + | + | −6 | Small | Small | Small | + | + | + | 0 | 0 | + | + | Normal |
| II ♀ | 36 | 0 | 36 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | + | + | +7 | + | + | + | 0 | 0 | 0 | 0 | 0 | 0 | + | Normal |
| III ♀ † | 8 | 2 | 8 | + | 0 | 0 | 0 | 0 | 0 | 0 | . . | . . | + | . . . . | Small | Small | Small | + | + | + | + | + | + | + | LAD* P-R + |
| IV ♂ | 22 | 5 | 22 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | 0 | . . . . | Small | 0 | 0 | + | + | + | + | 0 | 0 | + | Normal |
| V ♂ | 24 | 3 | 23 | 0 | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 | 0 | . . . . | Small | Small | Small | 0 | 0 | 0 | + | + | 0 | + | Normal |
| VI ♂ | 47 | 7 | 47 | + | 0 | 0 | 0 | + | 0 | + | 0 | 0 | 0 | +15 | Small | Small | Small | + | 0 | 0 | 0 | 0 | 0 | + | LAD* |
| VII ♂ † | 4 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | . . . . | Small | 0 | 0 | + | + | . . | 0 | 0 | 0 | + | |
| VIII ♂ † | 14 | 1 | 14 | + | 0 | + | 0 | 0 | 0 | 0 | 0 | + | 0 | . . . . | Small | Small | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | Normal |
| XI ♀ | 24 | 6 | 24 | 0 | 0 | 0 | 0 | + | + | + | + | + | + | +8 | Small | Small | Small | + | + | + | + | 0 | 0 | + | Normal |
| X ♀ † | 10 | 1 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | . . . . | + | + | + | 0 | 0 | 0 | 0 | 0 | 0 | + | |
| XI ♂ | 15 | 24 | 15 | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 | + | 0 | . . . . | 0 | 0 | 0 | + | + | + | + | 0 | + | + | Normal |
| XII ♂ | 16 | 48 | 16 | + | 0 | + | 0 | 0 | + | 0 | 0 | 0 | 0 | . . . . | 0 | 0 | 0 | 0 | 0 | + | 0 | + | 0 | + | LAD* |
| XIII ♂ | 31 | 0 | 31 | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | . . . . | + | 0 | 0 | + | + | + | + | 0 | 0 | + | Normal |
| XIV ♂ | 26 | 0 | 21 | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | +4 | + | 0 | 0 | + | + | + | + | + | 0 | + | Normal |

* LAD = Left axis deviation.

† Patients of St. Louis Children's Hospital. Case VII has been published.[14]

‡ These cases will be discussed in a separate publication.

Table modified after Stewart and Bailey.[4]

These data are compatible with (1) aortic insufficiency, (2) interference in blood flow to the lower extremities, (3) anomalous origin of the left subclavian artery and (4) constriction of the aorta distal to or at the site of origin of the left subclavian artery. The correctness of this interpretation was established at operation which confirmed the location of the coarctation.

Figure 3 (Case II) represents a subclinical case of coarctation. The patient was studied in the arms. With a large blood pressure cuff (19 cm. wide) the values as reported in Table II were obtained. The amplitude of the pulse wave of the right finger was 3.5 mm. as compared with 2 mm. of the right foot, not a striking difference. However, the direct systolic pressure in the right brachial artery was 193 mm. Hg and the diastolic 116 while that of the right femoral was 162 mm. Hg and the diastolic 107. These findings were interpreted as com-

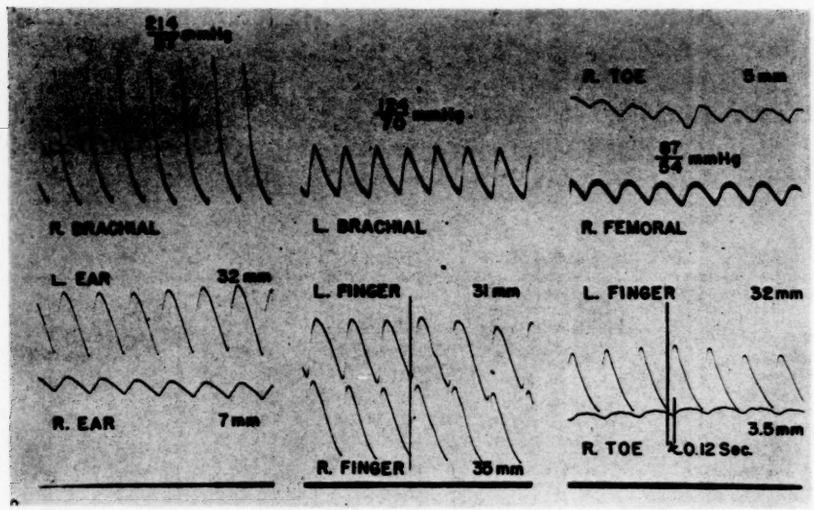


FIG. 2. Case III, N. P. Photographic records of arterial pressure and plethysmograms in an eight year old child with aortic insufficiency and coarctation of the aorta. The left subclavian artery arose at the site of the coarctation. Note the difference in blood pressure between the right and left brachial arteries and the femoral. The plethysmogram of the right second toe was taken simultaneously with the femoral arterial pressure. A large dilated vessel in the neck, which may have been an aneurysm, may account for the difference in pulses between the two ears. The similarity of the amplitude of the pulses in the two fingers is unexplained, but there is a slight delay in the left as compared with the right. In spite of the aortic insufficiency the pulse wave velocity between the finger and toe was prolonged. The camera speed was 25 mm. per second.

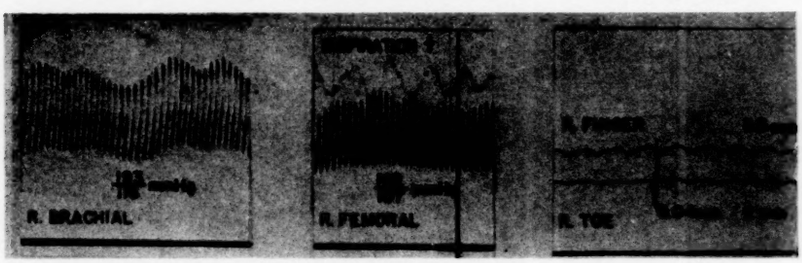


FIG. 3. Case II, O. P. Record reads from right to left; speed of camera 5 mm. per second. The patient exhibited a very slight degree of coarctation of the aorta according to retrograde arteriograms. The systolic pressure in the femoral artery is lower than that in the brachial, but the velocity of the pulse wave from finger to toe, if anything, is elevated. This patient also suffered from arterial hypertension.

patible with a mild coarctation of the aorta and arterial hypertension. The velocity of the pulse wave from finger to toe was 14.5 M. per second which is inconsistent with a coarctation of any pronounced degree. Aortic arteriography confirmed this impression.

The most consistent finding was a lower systolic pressure in the femoral than in the brachial artery. (Table II.) In only one case (W. W.) was there a marked difference in diastolic pressure. This was found in a fifteen year old boy who complained of intermittent claudication in the legs. He was short in stature. The essential findings (Fig. 4) were: (1) a systolic pressure of 205 mm. Hg in the brachial artery and 75 in the femoral, (2) a diastolic pressure of 92 mm. Hg in the brachial and 50 in the femoral, (3) diminution in the amplitude of the pulse in the left ear as compared to the right, (4) a delay in the appearance of the pulse in the scrotum of 0.18 seconds as compared to the ear (pulse wave velocity of 1.5 M. per second) and (5) absence of

pulsation in the toes. A double peak in the tracing made from the brachial artery was also noticed. These findings were consistent with a severe coarctation. The low amplitude of the pulse in the left ear was assumed to have been the result of retrograde aortic of constriction as indicated by a lower systolic pressure in the femoral artery. The pulse wave velocity, ear to scrotum, was now 3.3 M. per second and that of the finger to toe 5.3 to 5.9 M. per second (approximately within normal limits).

TABLE II

SPECIAL STUDIES IN PATIENTS WITH COARCTATION OF THE AORTA

| Case No. | Blood Pressure* (mm. Hg) | | | | Difference in Direct Arterial Blood Pressure Brachial-Femoral (mm. Hg) | | Photoelectric Plethysmography (amplitude in mm.) | | | | | | Pulse Wave Velocity (m./sec.) (Fingers to Toes) | Confirmation of Diagnosis | | | Type of Coarctation and Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Right Arm | Left Arm | Right Leg | Left Leg | Systolic | Diastolic | Hand | Toes | Ear Lobe | Scrotum | Left Hand | Right Hand | | Angiocardiography‡ | Aortic Arteriography‡ | Operation‖ | |
| I | 136/62 | 134/50 | 98/84? | 112/94 | | | | | | | | | | | | | |
| | *143/60* | ..... | *90/57* | ..... | − 53 | − 3 | 11.5 | 2 | ... | ... | ... | ... | 4.5 | .. | + | .. | Adult |
| II | 184/115 | 190/118 | 149/113 | ..... | | | | | | | | | | | | | |
| | *193/116* | ..... | *162/107* | ..... | − 31 | − 9 | 3.5 | 2 | ... | ... | ... | ... | 14.5 | .. | + | .. | Adult, arterial hypertension |
| III | 180/110-0 | 110/70 | Not obtainable | | | | | | | | | | | | | | |
| | *214/57* | *124/70* | *87/54* | ..... | −127 | − 3 | 32 | 3.5 | ... | ... | 31 | 35 | 3.8 | + | + | + | Adult, rheumatic heart disease |
| IV | 174/90 | 164/88 | Not obtainable | | | | | | | | | | | | | | |
| | *185/95* | ..... | *118/90* | ..... | − 67 | − 5 | 9 | 1 | 14 | 1 | 9 | 10 | Not obtainable | .. | + | .. | Adult, right undescended testis removed at the age of seventeen |
| V | 160/85 | 160/82 | 130/90 | 130/95 | | | | | | | | | | | | | |
| | *164/78* | ..... | *107/75* | ..... | − 57 | − 3 | ..... | | 25 | 5 | ... | ... | .... | .. | .. | .. | Adult, ? interventricular septal defect |
| VI | 184/92 | 182/90 | 140/115 | 130/110 | | | | | | | | | | | | | |
| | *200/80* | ..... | *110/70* | ..... | − 90 | −10 | 6 | 1 | 38 | 4 | ... | ... | 4.9 | .. | .. | .. | Adult |
| VII | 118/70 | 100/? | Not obtainable | | | | | | | | | | | | | | |
| | *125/70* | ..... | *70/65* | ..... | − 55 | − 5 | 6 | 2.5 | 24 | 3 | 5 | 8 | 3.3 | + | .. | + | Infantile, not resectable |
| VIII | 90/70 | 110/80 | 120/84? | 124/80? | | | | | | | | | | | | | |
| | *95/62* | ..... | *90/63* | ..... | − 5 | + 1 | 7.5 | 3 | 7 | 5 | 12 | 8 | 3.7 | + | + | .. | Adult |
| IX | 170/112 | 172/104 | Not obtainable | | | | | | | | | | | | | | |
| | *113/75*† | ..... | *132/78*† | ..... | + 19† | + 3† | ..... | | ... | ... | ... | ... | 10† | .. | .. | + | Adult, lumen 2 mm. in diameter |
| X | 118/78 | 102/76 | 152/118 | 148/102 | | | 6 | 8† | ... | ... | 6 | 4† | | | | | |
| | *135/70* | ..... | *125/70* | ..... | − 10 | 0 | 16 | 4 | ... | ... | 10 | 17 | .... | + | .. | .. | Not determined |
| XI | 188/90 | 190/94-60 | Not obtainable | | | | | | | | | | | | | | |
| | *205/92* | ..... | *75/50* | ..... | −130 | −42 | 9 | 0 | 36 | 4 | 10 | 18 | Not obtainable | .. | + | + | Adult, lumen 1 mm. in diameter |
| XII | 240/116 | 230/110 | Not obtainable | 94/86 | | | | | | | | | | | | | |
| | *195/115*§ | ..... | *134/107*§ | ..... | − 61 | − 8 | 17 | 0 | 31 | 3 | 9 | 10 | Not obtainable | .. | 0 | + | Stenosis above renal arteries by calcified thrombus |
| XIII | 180/95 | 178/98 | Not obtainable | | | | | | | | | | | | | | |
| | *170/90* | ..... | *105/75* | ..... | − 65 | −15 | 4 | 1 | 20 | 2 | 4 | 4 | 5.4 | .. | + | + | Adult, not resectable |
| XIV | 184/98 | 190/100 | Not obtainable | | | | | | | | | | | | | | |
| | *173/83* | ..... | *95/70* | ..... | − 78 | −13 | 6 | 0.5 | 18 | 3 | 6 | 6 | 3.0 | .. | + | + | Adult, lumen 2 mm. |

* Upper readings by auscultatory method. Lower readings (in italics) by direct arterial puncture.
† Eleven months postoperative.
‡ Performed by Drs. Thomas H. Burford and Merl J. Carson of Depts. of Surgery and Pediatrics.
§ Patient under general anesthesia.
‖ Performed by Dr. Thomas H. Burford.

arteriography done a few days previously which required incision and repair of the left carotid artery.

These findings were confirmed at operation. A lumen of 1 mm. was found at the site of constriction. Six days later the patient was restudied. The double systolic peak of the pulse contour had disappeared and pulsations were now visible in the scrotum and toes. There was still evidence

Results of the study of the nine other patients were similar. (Table II.) Diastolic pressures in the legs, with the exception of Case XI, were from 0 to 15 mm. Hg lower than those in the arms. In seven of the patients it was 5 mm. or less. Diastolic hypertension (90 mm. or more) was present in the legs in only three patients; one of them, with the very mild coarctation, undoubtedly suffered from generalized arte-

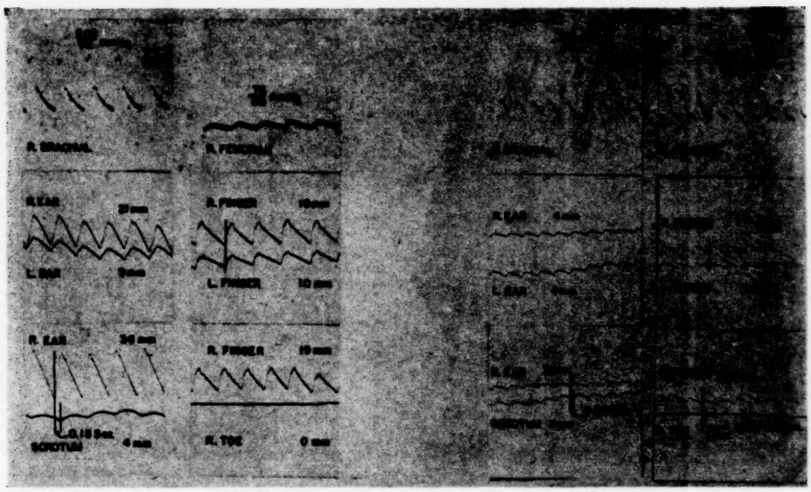

FIG. 4. Case XI, W. W. Photographic records of arterial pressure and photoelectric plethysmograms before (on the left) and after operation (on the right) for severe coarctation of the aorta. Note the very small pulsation in the femoral artery, toe and scrotum before operation. The difference in pulsations between the right ear and left may be due to involvement of the left carotid artery, which was opened three days previously for retrograde arteriography. After operation the changes are in the direction of normal. The pulse wave velocity between ear and scrotum is now within normal limits. There is, however, still a slight degree of coarctation as indicated by the differences of systolic pressure between the brachial and femoral arteries.

rial hypertension. (Case XI, Stewart and Bailey.)[4] Another (Case XII) was found at autopsy to have obstruction of his aorta caused by a massive deposit of calcium just above the renal arteries. Elevation of the diastolic pressure was present in the arms but not in the legs in two other cases. The postoperative findings in one (Case IX) were normal.*

Use of the auscultatory method for obtaining blood pressure in the legs gave erroneously high readings of diastolic pressure in six cases; levels were unobtainable in eight.

The amplitude of the pulse wave in the ear lobe appeared to be larger in four patients with coarctation of the aorta than in normal subjects or in those suffering from arterial hypertension of other causes. That in the finger was higher in seven patients. While the series is admittedly small, these findings indicate a difference in degree of vascular activity in these areas in certain cases of coarctation.

* Eight additional cases have been studied, only one of which had diastolic hypertension in the legs.

## COMMENTS

Only one Hamilton manometer was used to record the brachial and femoral arterial pressures. It is realized that simultaneous recordings would have been more desirable but the values obtained by subsequent measurements from one and then another extremity will give sufficiently accurate determinations for the differences found in coarctation of the aorta. The advantages of direct arterial puncture have been brought out in several instances. In severe coarctation the femoral pressure is often not obtainable by the auscultatory method. In the less severe cases a falsely high femoral pressure may be recorded. This was so in six of our patients. Only by direct arterial puncture can one obtain the true value and when this is done the milder cases of coarctation are readily established. Plethysmography offers confirmatory evidence.

The pathogenesis of the hypertension in coarctation of the aorta is controversial. That it is due to a general increase in arterial tone throughout the body has been

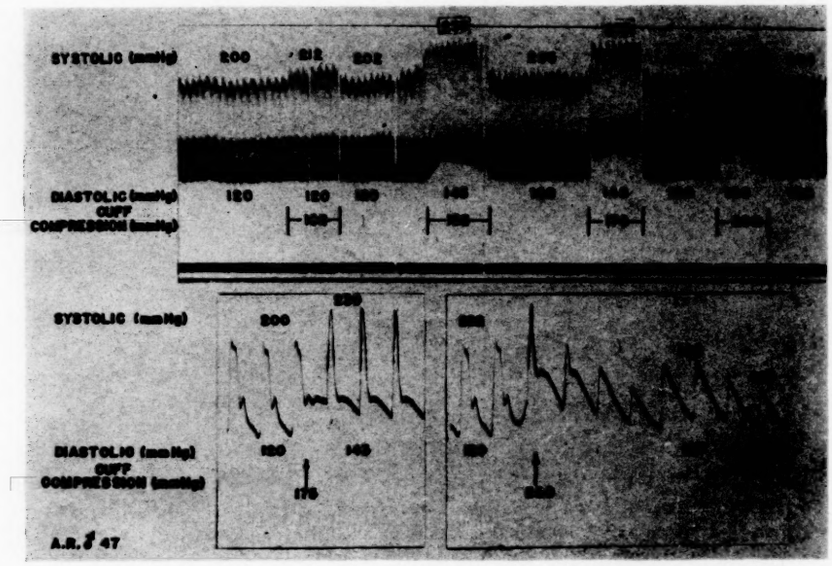


FIG. 5. A. R., the effect of partial occlusion of the brachial artery by a cuff upon blood pressure distal to the occlusion. In the upper curves the camera was moving at the rate of 1.25 mm. per second; the lower at 25 mm. per second. The figures at the top of the photograph refer to systolic pressure, those below to diastolic pressure and those between the vertical lines to compression of the cuff. Note the immediate rise of blood pressure when cuff compression is suddenly applied. Changes in the contour of the pulse wave are obvious (see text). At the high compressions the pulse wave appears similar to that seen in coarctation of the aorta. (Figs. 1, 2 and 4.)

advocated by Steele.[5,6] That it is due to the mechanical effects of the lesion was suggested again by Hull[7] and Bing.[16] In the cases presented there is evidence that both mechanisms may be involved. Diastolic hypertension in the legs, which is usually accepted as evidence of generalized arteriolar constriction, was present in only two patients. One of them showed a lesion just above the renal arteries which was a counterpart of the experiment of Steele.[8] It is a matter of interest that the diastolic pressure in the femoral artery was less than 60 mm. Hg in three patients, 60 to 80 mm. in seven patients and 80 to 90 mm. in none. The fact that the amplitude of the pulse wave in the upper part of the body was often higher (eight cases) than that seen in either uncomplicated hypertension or in normal subjects is further evidence for a mechanical factor being present. On the other hand, a low magnitude of the pulse similar to that seen in generalized hypertension was present in four cases, evidence for generalized vasoconstriction.

Hull[7] has recently suggested an interesting experiment involving the use of two cuffs on the arm. The upper cuff was inflated to a level just above diastolic pressure and the lower used to measure blood pressure. Under these conditions diastolic pressure was observed to rise slightly and the systolic to fall. Wilkins and Bradley measured the changes in brachial arterial and venous pressure distal to a cuff by Hamilton manometers.[9] The resultant systolic and diastolic pressure distal to the cuff was variable depending upon the amount of compression and the blood flow in the remaining part of the extremity. At certain critical supradiastolic levels of pressure in the cuff both systolic and diastolic pressure rose and blood flow increased. This experiment was repeated in six subjects, three of them with arterial hypertension, two with coarctation of the aorta and one with a normal blood pressure. When the cuff was inflated to various levels in increments of 25 mm. Hg, the results were similar except that the change was much greater in hypertensive

subjects. At levels of partial occlusion above diastolic pressure both systolic and diastolic levels were observed to rise significantly on the next beat after occlusion. (Fig. 5, Table III.) At higher pressures, of course, systolic fell and diastolic did not. The contours of the pulses then approached those seen in coarctation.

The rate of rise of the pulse also increased when the cuff was inflated above diastolic pressure, a finding first described by Erlanger.[10] This suggested that our results could be explained by the "breaker phenomenon" as proposed by Bramwell.[11] When a sea wave passes from deep water toward a beach, its crest travels faster than its trough, and the wave eventually breaks. The "beach" in this case is represented by the flattened artery under the cuff, which may so alter the wave front that it becomes steeper, and systolic pressure rises. Under these conditions diastolic pressure also rises, possibly because a turbulent flow has replaced one more or less smooth and the

TABLE III

EFFECT OF PARTIAL ARTERIAL OCCLUSION UPON BLOOD PRESSURE DISTAL TO POINT OF OCCLUSION (BRACHIAL ARTERY)

| Control Blood Pressure (mm. Hg) | Cuff Compression (mm. Hg) | Cuff Compression (blood pressure mm. Hg) | Cuff Compression (change) | Control Blood Pressure (mm. Hg) | Cuff Compression (mm. Hg) | Cuff Compression (blood pressure mm. Hg) | Cuff Compression (change) |
|---|---|---|---|---|---|---|---|
| A. K. ♂ 45 Arterial Hypertension | | | | A. R. ♂ 47 Arterial Hypertension | | | |
| 250/132 | 50 | 247/132 | − 3/0 | 200/120 | 100 | 212/120 | +12/0 |
| 260/132 | 75 | 260/132 | 0/0 | 202/120 | 150 | 235/145 | +33/+25 |
| 245/130 | 100 | 245/130 | 0/0 | 205/120 | 170 | 235/148 | +30/+28 |
| 233/127 | 125 | 255/130 | +22/+3 | 203/120 | 200 | 190/150 | −13/+30 |
| 247/130 | 150 | 270/143 | +23/+13 | 203/125 | 250 | 33* | |
| 240/125 | 175 | 270/152 | +30/+27 | | | | |
| 248/127 | 200 | 275/145 | +27/+18 | | | | |
| 250/128 | 225 | 218/136 | − 32/+8 | | | | |
| 235/132 | 250 | 50* | | | | | |
| M. C. ♀ 43 Arterial Hypertension (mild) | | | | D. W. ♂ 17 Normal | | | |
| 150/80 | 50 | 150/80 | 0/0 | 120/60 | 50 | 117/55 | − 3/−5 |
| 150/82 | 75 | 157/82 | + 7/0 | 119/60 | 75 | 120/60 | + 1/0 |
| 155/85 | 100 | 160/85 | + 5/0 | 115/55 | 100 | 120/70 | + 5/+15 |
| 150/85 | 125 | 165/95 | +15/+10 | 110/55 | 120 | 90/65 | −20/+10 |
| 160/90 | 150 | 145/100 | −15/+10 | 115/60 | 150 | 5* | |
| 160/90 | 175 | 30* | | | | | |
| H. W. ♂ 31 Coarctation of the Aorta | | | | W. R. ♂ 26 Coarctation of Aorta | | | |
| 170/92 | 90 | 170/90 | 0/−2 | 160/85 | 50 | 165/85 | + 5/0 |
| 162/90 | 100 | 170/95 | + 8/+5 | 160/87 | 75 | 165/85 | + 5/−2 |
| 167/93 | 118 | 175/95 | + 8/+2 | 159/84 | 95 | 170/85 | +11/+1 |
| 163/87 | 130 | 185/110 | + 22/+23 | 160/85 | 125 | 173/100 | +13/+15 |
| 165/90 | 150 | 165/115 | 0/+25 | 163/85 | 150 | 130/80 | −33/−5 |
| 160/93 | 175 | 53/45 | −107/−48 | 160/85 | 200 | 27* | |
| 170/90 | 200 | 15* | | | | | |

* Asystolic intra-arterial pressure thirty seconds after complete occlusion.[15]

Blood pressures are the average systolic and diastolic values for several beats. Although cuff compression appears to be greater than systolic pressure in patients D. W. and H. W., individual beats were at higher levels owing to natural variations.

coefficient of elasticity of the arterial wall under the cuff has been altered. Regurgitant flow is also abolished as suggested by Wilkins and Bradley. When the constriction is more severe, the form of the wave front alters further, becoming less steep, systolic pressure falling and diastolic pressure rising slightly. When the cuff is inflated to a level close to systolic pressure, both may become lower.

Attempts to reproduce this phenomenon in the femoral and renal arteries of dogs by means of a narrow clamp met with failure, probably because the distance over which the wave was altered was too small and the rigid clamp was not comparable to the elastic cuff. However, the narrow constriction of coarctation may so alter the aortic wave front as to cause some of the changes found in the femoral artery. All of these alterations were reproduced in the brachial artery by the experiment described.

Further, although controversial, evidence for the hypertension of coarctation of the aorta being different from the usual variety is offered by the insensitivity of these individuals to desoxycorticosterone acetate.[12] When this material is injected intravenously into patients with generalized arterial hypertension, a slow, sustained pressor response occurs. When it was given to six patients with coarctation of the aorta, no pressor response was elicited. One of them exhibited a high diastolic pressure and stenosis of the aorta above the renal artery.

It is possible to have a constriction of the aorta so severe as to prevent effectively the diastolic pressure in the leg from approximating that in the arm. (Case XI.) It is also possible to have a very mild coarctation. (Case II.) All gradations between these two extremes may be found. A decision as to the advisability of surgical repair of the defect depends in part upon the degree of coarctation and in part upon the extent of collateral circulation. It is obvious that a clamp applied to the thoracic aorta would alter hemodynamics severely and might be extremely hazardous to the patient if a large proportion of the blood were going through the constriction. Ordinarily we do not recommend surgery unless there is a marked difference (60 mm. Hg or more) in the systolic pressure of the brachial and femoral arteries as determined by direct puncture.

This method of study, while not new,[13] has been of considerable aid in evaluating the hemodynamics of the circulation in coarctation of the aorta. Because the condition sometimes can be corrected by surgery, the use of these methods is of more than academic interest.

## SUMMARY AND CONCLUSIONS

1. Fourteen cases of patients with coarctation of the aorta were studied by photoelectric plethysmography of peripheral parts and by direct measurements of brachial and femoral arterial blood pressure.
2. The hemodynamics of the circulation can be estimated by these methods, not only as an aid in locating the coarctation but in choosing patients suitable for surgery.
3. There is evidence that mechanical factors as well as humeral ones may operate to elevate blood pressure.

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# Acute Coronary Insufficiency Due to Pulmonary Embolism*

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THE interest aroused by the report of McGinn and White[1] on acute cor pulmonale led to many studies[2–10] of the electrocardiographic changes and other cardiac sequelae of embolism of the pulmonary artery. The electrocardiographic pattern described by McGinn and White is distinguished by a deep $S_1$ and $Q_3$, depression of the RS-T segment in Lead I, elevation of this segment in Lead III and inversion of $T_3$ or of $T_2$ and $T_3$, and was believed by these authors to be caused by acute right ventricular strain secondary to obstruction of the pulmonary artery. Our experience, however, indicates, as does that of several other authors,[4,8,11] that this pattern appears in a minority of patients with embolism of the pulmonary artery. In most of these patients the electrocardiographic changes consist chiefly of depression of the RS-T segment and inversion of the T wave in one or more leads, without a deep $S_1$ or $Q_3$. Since similar deviations follow acute coronary insufficiency precipitated by shock and hemorrhage,[12] it is apparent that such changes cannot be attributed solely to right ventricular strain.

Several factors may contribute to the cardiac and peripheral circulatory sequelae of embolization of the pulmonary artery. The purpose of this paper is to review briefly the physiologic aspects of the cardiovascular disturbances in pulmonary embolism and to evaluate the factors of right ventricular strain and failure, hyposystolic or forward failure, generalized anoxia or asphyxia and myocardial anoxia due to coronary insufficiency in the light of the clinical, electrocardiographic and anatomic findings. As we shall see, the predominant exciting factor is acute coronary insufficiency rather than right ventricular strain. Acute coronary insufficiency may be responsible not only for the electrocardiographic abnormalities but also for the acute myocardial changes in the left ventricle, which are far more serious than the involvement of the right ventricle.

*Acute coronary insufficiency* is the term we use to designate disproportion between nutritional requirements of the myocardium and its supply of coronary blood, resulting in absolute or relative deficiency of the coronary circulation. The term should not be construed to include thrombotic occlusion of the coronary artery.

Previously[12,13] we presented evidence that acute coronary insufficiency is a disease entity which is precipitated by several groups of factors. Severe exertion or emotional stress, tachycardia, hypertension, hyperthyroid crises, acute infections and drugs such as adrenalin and insulin, by elevating blood pressure, heart rate or cardiac output increase the work of the heart and thereby the myocardial requirement for blood, thus creating a relative coronary insufficiency. Shock, hemorrhage, hypotensive crises, acute heart failure, pulmonary embolism and coronary vaso-

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constriction may diminish the coronary blood flow by lowering the blood pressure and the cardiac output. The third group of factors consists of conditions which impair oxygenation of the blood or diminish its oxygen-carrying power; i.e., anesthesia, high altitude, carbon monoxide poisoning, acute anemia, pulmonary embolism, acute bronchial asthma and pulmonary insufficiency.

Acute coronary insufficiency is most likely to develop when predisposing factors which produce chronic deficiency of coronary blood flow with myocardial anoxia are present. These factors may be structural in nature, such as coronary arteriosclerosis, aortic valvular disease and cardiac hypertrophy; or non-structural, such as congestive heart failure and anemia.

When coronary insufficiency is sufficiently prolonged or severe, the ensuing myocardial ischemia and anoxia often cause acute degenerative or necrotic changes in the myocardium. These myocardial lesions vary in size from microscopic areas of necrosis to gross areas of infarction. They are characteristically focal, disseminated and situated in the subendocardial layer of the left ventricle particularly in the papillary muscles.

The electrocardiogram in acute coronary insufficiency is characterized by depression of the RS-T segment and inversion of the T wave in one or more leads, often in all leads, including the precordial. These deviations are due to the subendocardial localization of the myocardial ischemia. The electrocardiographic changes are reversible and may disappear with elemination of the precipitating factors and subsidence of the coronary insufficiency. Deep Q waves and elevation of the RS-T segment, typical of acute coronary occlusion, do not occur in acute coronary insufficiency.

## HISTORICAL SURVEY

Virchow[14] as early as 1856 attributed sudden death that occurred in a case of pulmonary embolism to "cardiac asphyxia and arrest" brought about by interference with the coronary blood flow. To explain the severe clinical symptoms caused by formation of small emboli in the lungs, it was suggested many years ago that reflexes which are mediated through the vagus nerve and elicited in the wall of the obstructed and distended pulmonary arteries cause widespread reflex pulmonary arteriolar constriction[15] and reflex stimulation of the respiratory center.[16] The latter is probably responsible for the tachypnea characteristic of these cases. Experimentally[7,16,17] this vagal reflex has been blocked by vagotomy or by administration of atropin and papaverine. It has also been demonstrated[18–20] that mechanical obstruction or ligation of the pulmonary artery for from 60 to 70 per cent of its cross-section area may not interfere significantly with the pulmonary circulation or produce pulmonary hypertension. On the other hand, distinct circulatory and cardiac effects are often noted following embolism even when the main pulmonary artery is uninvolved.[21] It is possible, therefore, that reflex constriction of the pulmonary arterioles may be an important factor in production of pulmonary hypertension in clinical pulmonary embolism. That vagal stimulation of considerable degree occurs in pulmonary embolism is evidenced by the not infrequent disturbances in sino-auricular and auriculo-ventricular conduction with resulting sinus arrest, sino-auricular block, nodal rhythm and auriculo-ventricular dissociation.[7]

Since 1933 a number of European workers[2,22–24] have alluded to the occurrence of a pulmonocoronary reflex mediated through the vagus nerve, which has been considered responsible for reflex vasoconstriction of the coronary arteries. Scherf and Schoenbrunner,[2] among the earliest proponents of this theory, ascribed precordial pain and other cardiac disturbances in pulmonary embolism to such reflex coronary vasoconstriction. However, more recent work[21,25] casts doubt upon the validity of this explanation. It has been found that bilateral cervical vagotomy does not abolish the electrocardiographic changes

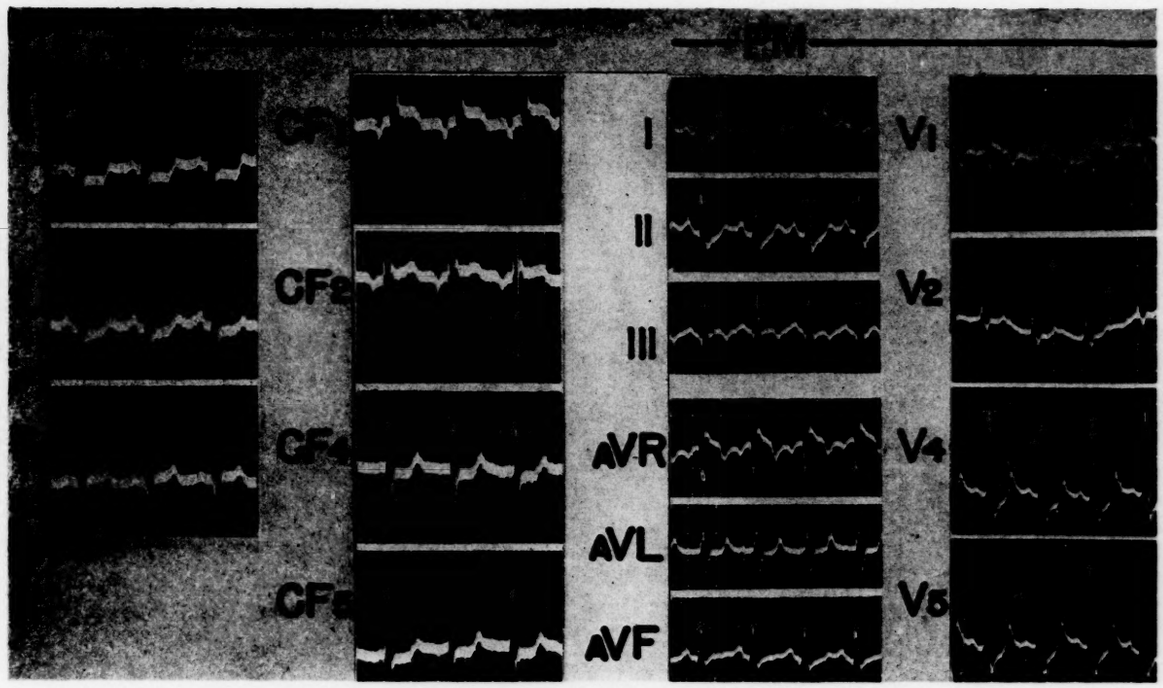
that appear following experimental pulmonary embolism. Furthermore, studies with Rein's flowmeter in experimental embolization[26] of the pulmonary artery show an increase in the minute volume flow in the right coronary artery, an observation that nullifies the theory of the existence of reflex constriction. Even in the presence of an increased coronary flow, coronary insufficiency and myocardial anoxia may be provoked if the increased flow is insufficient to compensate for the additional requirements of the ventricles and the increased work of the right side of the heart.

Nevertheless, changes of such degree occur in the hemodynamics of the pulmonary and systemic circulations that it is unnecessary to invoke the mechanism of reflex coronary constriction.[21] Eckardt[26] demonstrated that embolism of the pulmonary artery and increased pressure in the pulmonary artery are followed by diminution in arterial pressure, transitory decrease in coronary blood flow and then sustained increased flow particularly in the right coronary artery. He ascribed the drop in systemic blood pressure to the mechanical and reflex obstruction of the pulmonary blood flow, decreased return to the left ventricle and diminished cardiac output. This mechanism constitutes an important basis for forward failure of the left ventricle and coronary insufficiency in pulmonary embolism.[27] In 1937 Daly and his coworkers[28] and Schweigk[29] independently discovered a reflex relationship between the pulmonary and the systemic circulations. They showed that in animals with independent circulation in the pulmonary and systemic circuits, elevation of pulmonary artery pressure lowered systemic arterial pressure, independent of variations in venous return or cardiac output. In dogs this reflex effect was abolished by section of the cervical vagosympathetic nerves. Subsequent investigators[7,30] confirmed the existence of this reflex depressor mechanism and showed that it was the basis for the fall in systemic blood pressure and shock which occur in clinical pulmonary embolism. In their recent review of cardiodynamics of experimental pulmonary embolism Megibow, Katz and Steinitz[21] state that increased pressure in the pulmonary artery and the right ventricle leads to increased work of the right side of the heart, diminished coronary blood flow, coronary insufficiency and gradual or rapid heart failure.

There are numerous reports[5,7,27,31–33] of electrocardiographic changes observed following experimental pulmonary embolism and compression of the pulmonary artery. Although the deviations noted were not uniform, a large percentage of the electrocardiograms showed changes in the RS-T interval and T wave which could be attributed to coronary insufficiency and myocardial anoxemia.

Anatomic studies in both experimental and clinical pulmonary embolism afford corroborative evidence of the role played by coronary insufficiency and myocardial anoxia in this condition. Following experimental production of pulmonary embolism, Buchner and his associates[34] found focal areas of myomalacia in the right ventricle which they believed were due to coronary insufficiency. They reasoned that right ventricular dilatation and failure diminished blood flow in the right coronary artery; this resulted in ischemia, anoxia and necrosis of the right ventricular myocardium.

More recently Horn, Dack and Friedberg[6] observed acute myocardial changes in approximately 20 per cent of forty-two fatal cases of pulmonary embolism. In none of these cases was there a history of recent coronary occlusion. In an earlier study of myocardial infarction without acute coronary occlusion Friedberg and Horn[35] found that approximately one-fourth of the cases of infarction occurred in patients dying of recurrent embolism of the pulmonary artery. The myomalacia observed in the two studies was generally focal and subendocardial, localized in the left ventricle and was attributed to the effect of shock and anoxemia on the coronary circulation. In two of these cases focal myocardial necrosis was found




1A

FIG. 1A. E. V., a female, age forty years, experienced epigastric pain fifteen days after bilateral salpingo-oophorectomy. Seven hours later peripheral collapse developed and she died two hours thereafter. Autopsy revealed bilateral pulmonary embolism of the right main and left lower lobe branches. The coronary arteries were normal. The heart was grossly normal except for mottling of the posterior papillary muscle of the left ventricle. Microscopic examination in this area revealed focal myonecrosis (Fig. 1B.). Electrocardiogram taken soon after the onset of symptoms in the morning (A.M.) showed a small $S_1$ and deep $Q_3$, depression of RS-T in Leads I, II, $CF_4$ and $CF_5$ and elevation in Leads III and $CF_1$. At this time differentiation could not be made between acute cor pulmonale and acute posterior wall infarction due to coronary occlusion. The record taken several hours later in the afternoon (P.M.), however, showed the pattern of acute cor pulmonale, characterized by prominent S waves in Leads I, II, $V_4$ and $V_5$, small $Q_3$, prominent R and elevated RS-T in Leads AVR and $V_1$ and depressed RS-T in Leads I, II, $V_4$ and $V_5$ and an inverted $T_3$. It is of interest that myocardial ischemic changes secondary to acute coronary insufficiency developed in the presence of the classical cor pulmonale pattern in the electrocardiogram.

also in the right ventricle. Isolated right ventricular necrosis was not observed. From these observations it may be concluded (1) that coronary insufficiency following pulmonary embolism is generalized, affecting the left coronary artery as well as the right and (2) that the left ventricle is more susceptible than the right to the effect of coronary insufficiency.

Subsequently Currens and Barnes[9,10] found four cases of recent myocardial infarction without acute coronary occlusion among thirty fatal cases of pulmonary embolism. In three of the four instances infarction involved both ventricles. These authors also attributed the infarction to coronary insufficiency resulting from shock and increased pressure within the right side of the heart.

## MATERIAL

The present report is based on clinical and pathologic study of forty-one consecutive fatal cases of pulmonary embolism. In all cases one or more electrocardiograms were obtained following occurrence of the pulmonary embolism. The clinical status of the patients and the electrocardiograms obtained during the acute attacks were reviewed and correlated with the anatomic findings. Eighteen of the patients were men and twenty-three were women. Twenty-two were non-surgical cases; nineteen occurred postoperatively.

1B

FIG. 1B. Section of posterior papillary muscle of left ventricle showing loss of striation, lysis of fibrils, early necrosis and reactive polymorphonuclear leukocyte infiltration. These represent early ischemic myocardial alterations incident to acute coronary insufficiency which resulted from shock and diminished coronary blood flow. Although the insufficiency was of relatively short duration, it was sufficiently severe to have produced focal myonecrosis even in the presence of normal coronary arteries.

## RESULTS

*Electrocardiographic Findings.* The electrocardiograms were classified in four groups: Group I comprised fifteen cases presenting the general pattern of acute cor pulmonale; Group II, seventeen cases which presented the electrocardiographic deviations associated with coronary insufficiency, i.e., RS-T depressions and T wave inversions; Group III, six cases with atypical electrocardiographic changes which did not fall into either one of the first two groups; Group IV, three cases in which the electrocardiograms showed little or no variation from the tracings made before embolization occurred.

*Group I—Cor Pulmonale Pattern.* Eight patients presented the electrocardiographic pattern of acute cor pulmonale, that is, deep $S_1$ and $Q_3$, depressed RS-T in Lead I, elevated RS-T in Lead III and inverted $T_3$. (Fig. 1A.) In three other patients the pattern was similar except for the absence of a deep $S_1$. The remaining three patients presented deep $S_1$ and $Q_3$ but changes in the RS-T segment or T wave were absent. The T wave was inverted in Lead II in one case and in another it was inverted in $CF_4$. Atypical right bundle branch block was observed in three of the fifteen patients.*

*Group II—Coronary Insufficiency Pattern.* Electrocardiograms of this group disclosed depression of the RS-T segment and inversion of the T wave in one or more leads. (Fig. 2.) In ten cases the deviations occurred in all four or in three of the four leads; it was more common in Lead I than in Lead III. In five cases the RS-T segment was slightly elevated in Lead III. Depression of the RS-T segment occurred without T wave inversions in eight cases, but inverted T waves unaccompanied by RS-T deviations were infrequent occurring only twice. In three cases a small $S_1$ or $S_1$ and $Q_3$ were suggestive of acute cor pulmonale.

*Group III—Atypical Electrocardiographic Changes.* Six patients presented atypical acute electrocardiographic changes. In four of these intraventricular or bundle branch block was present prior to the pulmonary embolism and miscellaneous abnormalities involving the RS-T segment or T wave appeared subsequently. The RS-T segment was elevated in all leads in one case, in Leads I and II in another case and in Lead III in a third case. These atypical electrocardiographic changes were obviously related to the conditions underlying the abnormal records which antedated the embolic incidents.

*Group IV—No Acute Electrocardiographic Changes.* In the three cases in this group the electrocardiograms made following embolism of the pulmonary artery did not differ materially from the previous abnormal records which were the result of long-standing heart disease.

*Associated Electrocardiographic Changes.* Intraventricular conduction disturbances may appear following embolism of the pulmo-

* In one case in which multiple precordial and unipolar leads were recorded the RS-T segment was depressed over the left side of the precordium ($V_4$ to $V_6$) and elevated over the right side of the precordium ($V_1$) and in the unipolar lead from the right arm (VR). We have observed a similar pattern in acute coronary occlusion with posterior wall infarction and in acute coronary insufficiency from any cause.

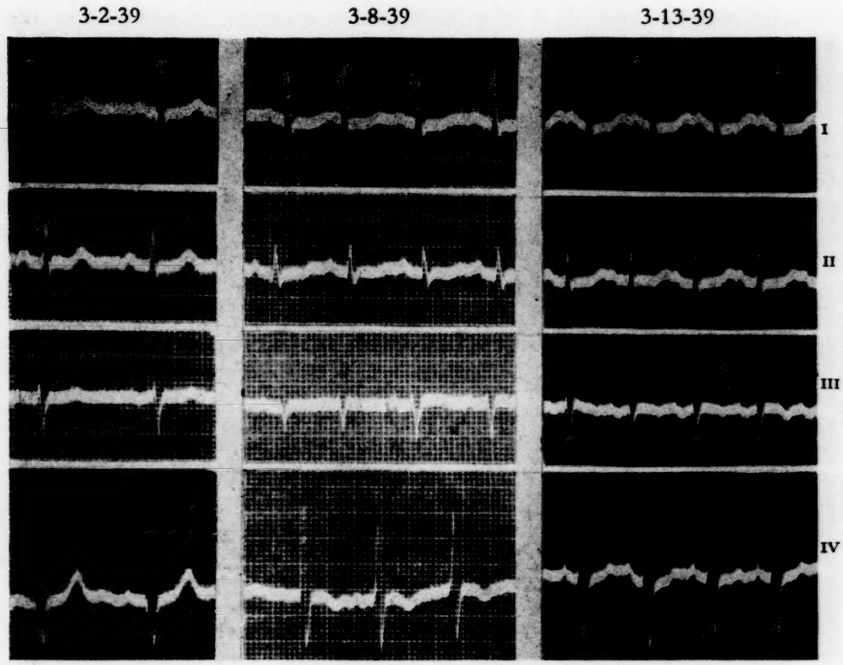



FIG. 2. J. K., a seventy-one year old man developed acute pulmonary artery embolism on March 8th, four days after resection of a carcinoma of the rectum. The patient died on March 14th. Autopsy revealed an embolic occlusion of the left main pulmonary artery. The coronary arteries were patent. The myocardium showed focal fibrosis and there were no acute changes either on gross or microscopic examination. The electrocardiogram taken prior to the embolic episode was normal except for left axis deviation. On March 8th, several hours after the onset of embolism, the S-T segment became depressed and the T wave semi-inverted in Leads I, II and $CF_4$. The record on March 13th was practically the same. These changes are those of acute coronary insufficiency.

nary artery,[36] usually within the first twenty-four to thirty-six hours. The intraventricular block is generally of the atypical right bundle branch block type; it may be transient. Atypical right bundle branch block developed in three of the cases in Group I (cor pulmonale) and persisted until death intervened early in the attack. In two other cases a left and a right bundle branch block pattern antedated the embolism.

Well defined right axis deviation was present in only five cases, three in Group I and two in Group II. Left axis deviation, on the other hand, appeared in eleven cases. In the majority of the latter the axis deviation preceded the embolic episode and was believed to have resulted from previous hypertensive and arteriosclerotic heart disease. (Figs. 4A and 5.)

Cardiac arrhythmias were observed in seven cases. Auricular tachycardia occurred twice, auricular fibrillation once and heart block once. In the latter case there was associated sino-auricular block and ventricular fibrillation occurred terminally. Similar arrhythmias have been observed in pulmonary embolism experimentally produced.[7,33,37]

The influence of various predisposing and precipitating factors in Groups I and II was evaluated. These included age, sex, antecedent cardiac disease, right ventricular strain and other anatomic changes observed during postmortem examination.

*Age and Sex Incidence.* There was a slightly higher incidence of women than men in the series and also in the individual groups, but the sex of the patients and the electrocardiographic pattern following pulmonary embolism were not apparently associated. On the other hand, the age of

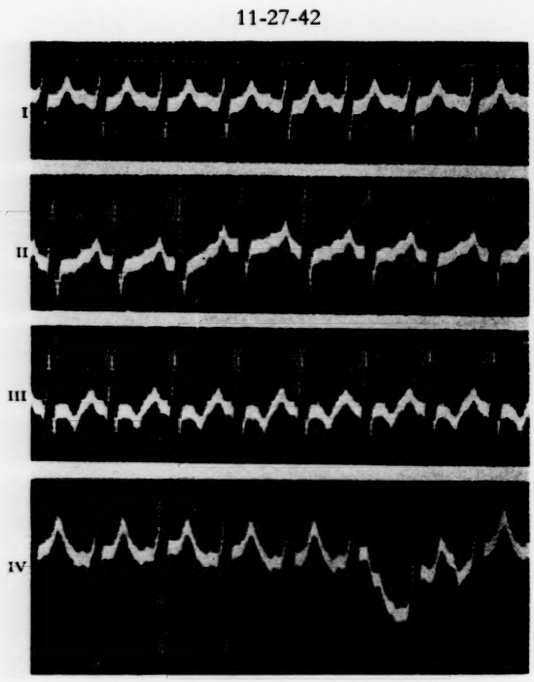
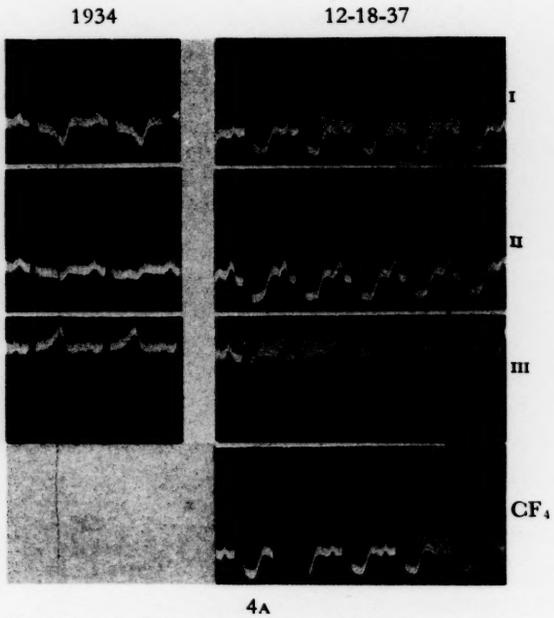



FIG. 3. E. P. was an eighteen year old boy with recurrent pulmonary embolism of two weeks' duration. A massive embolism occurred several hours prior to admission and ended fatally during an attempted pulmonary artery embolectomy. Autopsy revealed emboli to variously sized pulmonary artery branches with associated multiple pulmonary infarcts. The origin of the emboli was undetermined. The electrocardiogram showed the cor pulmonale pattern characterized by right axis deviation, deep $S_1$ and $S_2$, semi-inverted $T_2$ and inverted $T_3$. It differs from the classical pattern in the absence of a prominent $Q_3$.

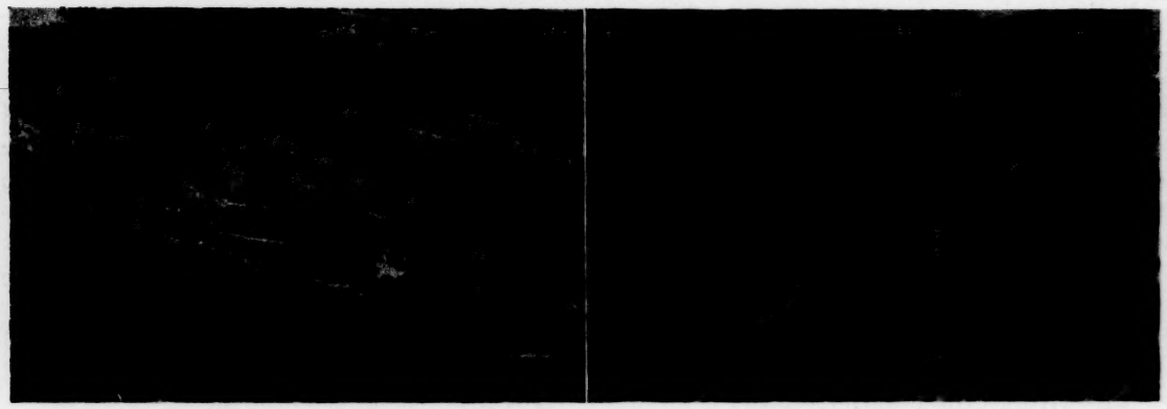



4A

FIG. 4A. A. F., a female aged fifty-four years, suffered with antecedent hypertensive heart disease of ten years' duration. Three weeks after a mild cerebrovascular accident she developed increasing dyspnea, restlessness, impaired heart sounds, drop in blood pressure and partial heart block. This was followed by tachycardia, tachypnea, labored breathing and death three days later. Autopsy showed multiple acute and organizing pulmonary artery emboli and pulmonary infarcts. The heart was hypertrophied, weighing 430 Gm.; the coronary arteries were normal. Focal subendocardial necrosis was noted involving the interventricular septum, anterior wall of the left ventricle and papillary muscles of both ventricles. The electrocardiogram taken in 1934 showed the typical "hypertensive" pattern of left ventricular enlargement, i.e., left axis deviation, high voltage QRS, RS-T depressed in Lead I and elevated in Lead III, $T_1$ deeply inverted and $T_2$ diphasic. On December 19, 1937, one day prior to death, there was striking RS-T depression in Leads I, II and $CF_4$ and slight depression in Lead III. These changes are characteristic of acute coronary insufficiency, the cause for the subendocardial myocardial necrosis. (Figs. 4B and C.)

the patient seemed to influence the electrocardiographic pattern. Of thirteen patients below the age of fifty, seven fell into Group I (cor pulmonale) and only two into Group II (coronary insufficiency). Of twenty-eight patients aged fifty years or more only eight fell into Group I while fifteen were in Group II. The coronary insufficiency pattern occurred more often in the older individuals in whom arteriosclerotic or hypertensive heart disease co-existed.

*Antecedent Cardiac Disease.* The foregoing observation was borne out by analysis of the cardiac status of the patients prior to occurrence of pulmonary embolism. One-half of the patients with acute cor pulmonale pattern (Group I) had clinical evidence of hypertension or coronary artery disease; three-fourths of the patients with coronary insufficiency (Group II) and all the patients with atypical electrocardiograms (Group III) had hypertension or arteriosclerosis. The classical picture of cor pulmonale appeared most often in the patients with previously normal hearts, whereas the antecedent cardiac disease seemed to be the predisposing factor in the development of coronary insufficiency. (Figs. 4 and 5.) When the electrocardiogram made prior to pulmonary



4B 4C

FIG. 4. B, photomicrograph of anterior wall of left ventricle showing multiple areas of focal acute and subacute necrosis and degeneration of the myocardium with reactive cellular infiltration by polymorphonuclear leukocytes and fibroblasts. In this case the shock, anoxemia and drop in blood pressure led to a decrease in coronary circulation. The heart was especially vulnerable to deficiency of coronary blood flow and associated myocardial anoxia because of the antecedent hypertension and cardiac hypertrophy. C, higher magnification of area of focal myonecrosis in left ventricle.

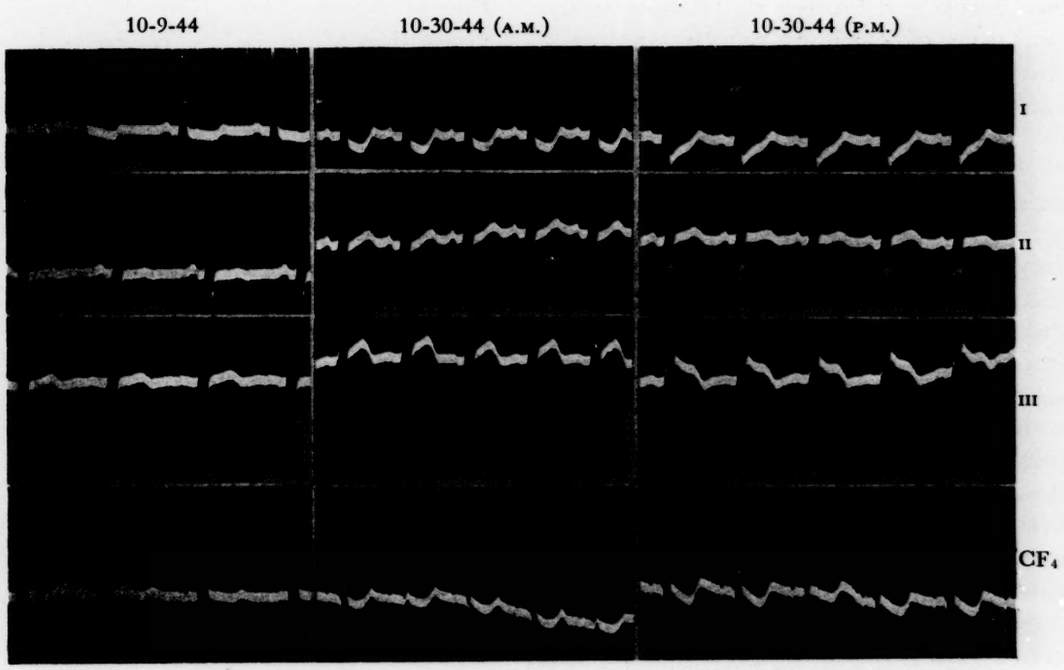



FIG. 5. P. K., a female aged seventy-two, developed shock, cardiac arrythmia, fall in blood pressure to 60/36, dyspnea and cyanosis on October 29th, four days after transverse colostomy. She died on October 31st. Autopsy revealed massive pulmonary embolism involving the main trunk and both branches. The heart showed only focal areas of fatty degeneration. The coronary arteries were atheromatous but patent. The preoperative electrocardiogram showed left axis deviation, high voltage QRS, $T_1$ inverted, $T_2$ and $T_4$ semi-inverted. This record suggests left ventricular enlargement and myocardial involvement. On October 30th, one day after the embolic episode, there were more striking RS-T depressions in Leads I and $CF_4$ and elevation in Lead III which persisted until death. These changes are indicative of acute coronary insufficiency. It is of interest that in the presence of a "left ventricular strain" pattern the acute coronary insufficiency intensified the S-T depression in Lead I and the elevation in Lead III.

embolism was very abnormal, the electrocardiographic changes following embolism were usually those of coronary insufficiency or, in a few instances, atypical. Furthermore, existing marked left axis deviation made development of the cor pulmonale pattern less likely. When left axis deviation was associated with RS-T deviations (depression in Lead I, elevation in Lead III), the latter were infrequently intensified by the coronary insufficiency. (Fig. 5.)

*Cardiac Enlargement.* Correlation of the electrocardiographic pattern with the actual weight of the heart corroborated the clinical observations. Distinct cardiac enlargement (heart weight 400 Gm. or over) was found in 14 per cent of the patients with cor pulmonale electrocardiograms and in 59 per cent of those with coronary insufficiency records, a finding that indicates the importance of cardiac hypertrophy as a predisposing factor in the development of coronary insufficiency following pulmonary embolism.

*Right Ventricular Strain.* Incidence and degree of dilatation of the right side of the heart was observed at necropsy in the thirty-two patients comprising Groups I and II. Dilatation of the right ventricle was found in seven of the fifteen cases of cor pulmonale and in eight of the seventeen cases of acute coronary insufficiency. Right ventricular dilatation was not, therefore, regularly associated with either a "cor pulmonale" or a "coronary insufficiency" electrocardiogram. As a matter of fact, the pattern of coronary insufficiency appeared most often in patients with marked dilatation of the chambers of the right side of the heart, a finding which suggests that coronary insufficiency and right ventricular strain may occur simultaneously following massive embolism of the pulmonary artery. That coronary insufficiency may be the dominant factor in the clinicopathologic abnormalities, however, is indicated by the myocardial damage found in such cases.

*Pathologic Myocardial Changes.* A detailed anatomic study of the heart was made in all cases. Many blocks of the ventricular walls including the papillary muscles were taken for microscopic study and the coronary arteries were sectioned at close intervals. Evidence of myocardial necrosis was found in ten of the cases (24 per cent): in three cases gross changes were present in the myocardium and in seven cases, histologic changes. Acute occlusion of a coronary artery was not seen in any of the hearts.

The gross myocardial changes consisted of focal, disseminated areas of yellowish-red mottling in the subendocardial layer of the myocardium involving especially the papillary muscles of the left ventricle. In one case the anterior wall of the left ventricle was involved, and in two cases both surfaces of the left ventricle were affected. In one of the latter cases there was also focal infarction of the right ventricle. Microscopic examination of the lesions revealed degenerative alteration of the muscle fibers, focal hemorrhage and necrosis. The latter had provoked reactive cellular infiltrates of polymorphonuclear leukocytes, histiocytes and fibroblasts. These lesions differed in no way from those observed in cases of acute coronary insufficiency precipitated by other factors, such as shock, drop in blood pressure and hemorrhage.[12]

Five of the cases of focal myocardial necrosis were in Group I, four in Group II and one in Group IV. In other words, acute myocardial changes were found among the patients with clinical signs of cor pulmonale as frequently as among those with clinical evidence of acute coronary insufficiency. The myocardial changes in the four cases of coronary insufficiency (Group II) were, however, decidedly more severe than the changes in the cases of cor pulmonale (Group I). In three of the four hearts of Group II gross infarction was fairly extensive (Figs. 4B and 4C); in the five hearts of Group I infarction was detected only on histologic examination.

The ten cases of focal myocardial infarction were analyzed with a view to determining the nature of the factors which had predisposed the patients to acute coronary

insufficiency. In eight cases evidence of antecedent arteriosclerotic or hypertensive heart disease was found. There was moderate to severe stenosis of the coronary arteries in four of the hearts. When the coronary arteries were patent, the hearts were distinctly hypertrophied and enlarged. Four patients had sustained multiple pulmonary lesions and had lived from two to three weeks following initial embolization. One patient with a heart normal in size and patent coronary arteries lived only nine hours. The embolism, however, involved all the branches of the pulmonary artery as well as the main stem, and the profound degree of shock and anoxemia produced intense coronary insufficiency despite absence of predisposing arteriosclerotic factors.

In summary, it may be said that coronary insufficiency and focal myocardial infarction had a tendency to follow pulmonary embolism in those cases in which there was pre-existing coronary arteriosclerosis or cardiac hypertrophy, particularly when the embolism was multiple and the duration of life following the onset was sufficiently long to permit development of anotomic myocardial changes.

## COMMENT

Analysis of forty-one fatal cases of embolism of the pulmonary artery indicates that acute coronary insufficiency is an important factor in determining the electrocardiographic picture and the myocardial effects that follow embolism. So much attention has been directed toward the right ventricular dilatation and strain following pulmonary embolism that sight has been lost of the fact that the left ventricle is affected deleteriously and often to a greater extent than the right ventricle. In our series the electrocardiographic pattern of acute coronary insufficiency occurred more often than did the pattern of cor pulmonale, and myocardial necrosis involved the left rather than the right ventricle.

The electrocardiographic and anatomic changes attributable to acute coronary insufficiency were found for the most part in the older individuals and in those with clinical or anatomic evidence of antecedent heart disease. In other words, acute coronary insufficiency is more likely to follow pulmonary embolism in patients with chronic coronary insufficiency than in those individuals who have previously been free of cardiac abnormalities. On the other hand, the classical cor pulmonale pattern and right ventricular strain occurred most often in those patients whose hearts were previously normal.

The mechanism underlying development of coronary insufficiency following embolism of the pulmonary artery can be explained by the known physiopathologic effects produced by obstruction of the pulmonary artery. Our observations offer clinico-pathologic evidence that the important exciting factors of the diminished coronary blood flow and myocardial anoxia are systemic shock, right ventricular dilatation, anoxemia and possibly reflex coronary vasoconstriction.

*Shock.* Shock was an almost universal feature in our series of cases. It occurred in patients with cor pulmonale as often as in those with coronary insufficiency; it was most severe in those patients in whom ischemic or anoxic changes of the myocardium developed. It has been stated[6,7,21,26,27,29] that obstruction of the pulmonary artery, as well as clinical pulmonary embolism, leads to lowering of systemic blood pressure, diminished venous return to the left ventricle, diminished left ventricular stroke output and shock. These circulatory disturbances eventually result in diminished coronary blood flow and nutritional disturbances in the myocardium of both ventricles but more particularly the left. When the shock is intense and prolonged and the coronary circulation has been impaired previously by coronary arteriosclerosis or cardiac hypertrophy, the myocardial anoxia may progress to focal degeneration or subendocardial necrosis in the myocardium. The site of the necrosis is usually the left ventricle.

*Right Ventricular Dilatation.* Both clinical and postmortem observations have demonstrated that acute dilatation and strain of the right ventricle is a common sequel to massive embolism of the pulmonary artery. Accentuation of the pulmonic second heart sound, right ventricular failure and the typical $S_1$ $Q_3$ pattern in the electrocardiogram are the usual clinical signs of right ventricular dilatation and strain.[38] In our series distinct right ventricular dilatation, often of a marked degree, was found at autopsy in approximately one-half of the cases.

It is significant that autopsy revealed that right ventricular dilatation occurred as frequently in cases with electrocardiographic records of coronary insufficiency as in those with records of right ventricular strain. Conversely, in half of the cases in which isolated right ventricular dilatation was found at autopsy, the electrocardiograms showed changes characteristic of acute coronary insufficiency. Furthermore, right ventricular strain was found in approximately half of the cases of focal myocardial infarction of the left ventricle. These observations afford further evidence that acute coronary insufficiency may be the dominant factor underlying the electrocardiographic changes and myocardial involvement even when right ventricular strain exists. It has been suggested[9,10] that right ventricular strain may contribute to the development of coronary insufficiency. This theory based on clinical grounds is in agreement with the observations of investigators[21,39] who found that following experimental obstruction of the pulmonary artery the increased right ventricular pressure was associated with diminution in coronary blood flow, particularly in the right coronary artery. Megibow, Katz and Steinitz[21] attributed the coronary insufficiency to extravascular compression of the Thebesian veins and interference with emptying of the coronary sinus and veins.

It might be assumed that in the presence of right ventricular strain, with resulting increase in nutritional requirements of the right ventricle, the right ventricle would be the site of predilection for the morphologic sequelae of acute coronary insufficiency. This theory seems to be borne out by the work of Buchner and his associates[34] who found that pulmonary embolism in animals induced right, rather than left, ventricular myomalacia. They attributed this result to diminution of flow in the right coronary artery. Currens and Barnes[10] reported one patient with isolated infarction of the right ventricle. In our series, however, involvement of the right ventricle was in all cases associated with involvement of the left. The fact that the left ventricle was affected much more frequently and to a much greater degree than the right ventricle suggests that the left ventricle is more susceptible than the right to acute coronary insufficiency, even when right ventricular strain and dilatation are present. The increase in ventricular pressure that follows embolism may produce greater diminution of blood flow in the right coronary artery than in the left coronary artery, thereby affecting chiefly the posterior wall. We believe, however, that this resemblance may be incidental and that right ventricular dilatation and cardiac rotation are important causes for this resemblance.

*Anoxemia.* The third precipitating factor of coronary insufficiency in pulmonary embolism is anoxemia. This is manifested clinically by dyspnea, tachypnea and cyanosis which result from obstruction of the pulmonary artery, diminished pulmonary blood flow and impaired oxygenation of the blood.

Anoxemia and asphyxia may produce anoxic changes in the myocardium of both the left and the right ventricles. In anoxemia arising from conditions other than pulmonary embolism, increase in coronary blood flow is provided by coronary vasodilatation,[40] but with pulmonary embolism the shock and right ventricular dilatation incident to the embolism produce absolute diminution of coronary blood flow. The affect of the anoxemia on the myocardium is thus intensified by the associated ischemia.

Anoxemia may be responsible for the electrocardiographic changes in pulmonary embolism particularly in the coronary insufficiency group, since the RS-T and T wave abnormalities produced by anoxemia and by coronary insufficiency are indistinguishable.[12,13,41] Similar RS-T and T wave changes have been observed in acute cor pulmonale not due to pulmonary embolism, for example, in acute bronchial asthma. Many years ago it was reported[42] that in animals identical electrocardiographic changes occurred in asphyxia, acute asthma and following clamping of the pulmonary artery. The changes in the RS-T segment and T waves which commonly occur during and immediately following an asthmatic paroxysm have been attributed to myocardial anoxia resulting either from diminished blood oxygen saturation[43] or from acute coronary insufficiency.[44] We have observed cases of bronchial asthma in which the severity and prolonged duration of the electrocardiographic changes suggested that the myocardial anoxia had produced myocardial infarction.

*Pulmocoronary Reflexes.* A fourth mechanism which may play a part in production of coronary insufficiency in pulmonary embolism is reflex coronary constriction mediated through the vagus nerve endings in the pulmonary arterial tree. There is no doubt that a reflex inhibitory effect on the heart may exert a considerable effect in pulmonary embolism[7] and that it may produce slowing of the heart from sino-auricular depression and lowered blood pressure. However, evidence is lacking that such activity can cause coronary vasoconstriction.

## SUMMARY

A study of forty-one consecutive fatal cases of pulmonary embolism confirmed by autopsy showed that acute coronary insufficiency is an important factor in determining the electrocardiographic and myocardial effects following embolism of the pulmonary artery. The electrocardiographic pattern of "acute cor pulmonale" (deep $S_1$ and $Q_3$, depressed RS-T in Lead I, elevated RS-T in Lead III and $T_3$ inversion) occurred in only a minority of cases. In the majority the electrocardiographic changes were those characteristic of acute coronary insufficiency, namely, RS-T depression and T wave inversion in one or more leads and often in all leads.

Antecedent hypertensive or arteriosclerotic heart disease and cardiac hypertrophy were important predisposing factors of acute coronary insufficiency. The classical cor pulmonale pattern was seen more often in patients with previously normal hearts. When the electrocardiogram prior to the embolism was very abnormal, the electrocardiographic changes were usually those of coronary insufficiency or, less often, atypical in character. Furthermore, the presence of marked left axis deviation made the development of the cor pulmonale pattern less likely.

Right ventricular dilatation was not regularly associated with either "cor pulmonale" or "coronary insufficiency" electrocardiogram. The pattern of coronary insufficiency was often noted in patients with marked dilatation of the chambers of the right side of the heart, a fact which suggests that coronary insufficiency and right ventricular strain may occur simultaneously following massive embolism of the pulmonary artery.

Changes indicative of myocardial necrosis or infarction resulting from acute coronary insufficiency were found in ten cases or 24 per cent. In three of these cases there were gross changes in the myocardium and in seven cases histologic changes. Acute occlusion of a coronary artery was not seen in any of the hearts. The most frequent sites of necrosis were the subendocardial layer of the left ventricle and the papillary muscles. The anterior and posterior walls of the left ventricle were involved with equal frequency. The right ventricle was involved in only one case, emphasizing the greater deleterious effect of pulmonary embolism on the left ventricle. Acute myocardial changes were found in cases with electrocardiograms indicative of cor pul-

monale as frequently as in cases with electrocardiographic signs of acute coronary insufficiency.

Coronary insufficiency following embolism of the pulmonary artery is caused by diminished coronary blood flow and myocardial anoxia which result from systemic shock, right ventricular dilatation, anoxemia and possible reflex vasoconstriction. The pathologic physiology and relative importance of these factors are discussed.

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# Auricular Fibrillation without Other Evidence of Heart Disease*

## *A Cause of Reversible Heart Failure*

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It is now well known that auricular fibrillation may occur in people without other evidence of organic heart disease. This is particularly true of the paroxysmal form of the irregularity for transient spells are frequently seen in individuals who are otherwise well. Even persistent auricular fibrillation lasting for months or years without any other evidence of organic disease, subjective or objective, has been observed occasionally. What has not been sufficiently appreciated is that such patients occasionally develop outspoken congestive heart failure and that all evidence of heart disease may disappear with complete return to a normal state if the gross irregularity can be restored to normal rhythm. In this sense there is a small but definite group of patients with moderate to advanced heart failure in whom the entire process is reversible under appropriate therapy. Finally, there is a strong suspicion, from the experience to be discussed, that some patients with irreversible congestive heart failure and auricular fibrillation started with an essentially normal heart but because of prolonged auricular fibrillation developed cardiac enlargement and heart failure. Such patients then may partially respond to digitalis and diuretics. They may develop hypertension or other cardiac complications and succumb, as most patients with organic heart disease do; this is often called chronic myocarditis with auricular fibrillation or instances of nonvalvular heart disease. It is inferred that these eventualities might have been delayed or prevented if the original arrhythmia had been rectified early enough.

One of the first cases of auricular fibrillation with congestive failure without other evidence of organic disease was reported by Gossage and Hicks.[1] Although postmortem examination showed hypertrophy and dilatation of the left ventricle, the authors believed that the heart originally had no organic abnormalities and that the hypertrophy was a consequence of the arrhythmia. Parkinson and Campbell[2] found no evidence of heart disease in 30 of their 200 patients with paroxysmal auricular fibrillation. There was no apparent cause for the irregularities in eighteen, and infection or toxic agents were thought to be the precipitating factors in the other twelve cases. Auricular fibrillation eventually became chronic in three of their patients with normal hearts. Fowler and Baldridge[3] reported seven cases of transient and three of persistent auricular fibrillation in young adults without evidence of heart disease. Mohler and Lintgen[4] found no apparent cause for auricular fibrillation in about 6.5 per cent of their 220 patients. Likewise, Friedlander and Levine[5] in 1934 reported thirty-five cases of auricular fibrillation and four of auricular flutter without evidence of heart disease. This comprised about 6 per cent of all their cases of auricular fibrillation. A similar group of forty-six cases of

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transient and three of chronic auricular fibrillation was published in 1936 by Orgain, Wolff and White.[6] It is apparent that auricular fibrillation, either transient or permanent, without organic disease is not at all rare and may be expected to occur in a little more than 5 per cent of all fibrillators.

What is more important is that the irregularity may precipitate congestive failure when the heart is otherwise normal. Although this study is not concerned with the development of anginal pain following paroxysmal rapid heart action, such a complication does occur and has been thoroughly discussed by Wolff.[7,8] In the case published by Gossage and Hicks[1] a twenty-three year old man developed progressive cardiac enlargement and chronic failure in spite of digitalization and died after running across a road eighteen and one-half months after the onset of his illness. Parkinson and Campbell's patient[2] was an athlete who developed paroxysmal fibrillation in 1912 at the age of twenty-four years. In 1920 the arrhythmia became permanent and two years later congestive failure appeared. At one time his life was saved by the intravenous administration of strophanthin, but he remained a cardiac invalid for the next three years despite digitalis therapy. In 1925 the cardiac mechanism was reverted to normal by quinidine which resulted in a complete recovery. Five years later the patient was engaging in vigorous sports without evidence of heart disease.

Brill[9] reported the case of a forty-three year old female who developed auricular fibrillation in 1935. Ten weeks later cardiac enlargement and congestive failure developed. After reversion to normal rhythm with 0.2 Gm. of quinidine the heart size returned to normal and the congestive failure disappeared. Ten years later this patient was well, showing no evidence of heart disease.[10] Trotter and Eden[11] reported the case of a forty-three year old man in whom auricular fibrillation without apparent cause produced congestive failure. Digitalis reverted the rhythm to normal and cured the heart failure. Seven years later permanent auricular fibrillation developed and within several months congestive symptoms recurred and could not be controlled adequately with digitalis. After total thyroidectomy, which was performed as a last resort, normal rhythm returned and all the symptoms disappeared. There was no gross or microscopic evidence of thyrotoxicosis in the gland.

Levine and Beeson[12] reported an instance in which severe congestive failure occurred after auricular fibrillation became permanent when there was no other evidence of heart disease. This patient was also cured by reversion to normal rhythm. (Case II.) It is evident from these isolated case reports that severe heart failure may be completely reversible in a small group of patients in which auricular fibrillation *per se* is the cause of the disability.

The purpose of this study was to investigate some of the changes in the dynamics of the circulation that appear to develop as a result of auricular fibrillation in patients who have no other evidence of heart disease, and to emphasize that the arrhythmia alone can be the cause of congestive heart failure. The clinical evidence brought forth also suggests that some cases of irreversible heart failure with auricular fibrillation may have started with an essentially sound heart and that the subsequent disability might have been prevented if normal rhythm had been restored by use of quinidine in the early stages of the arrhythmia.

## ABNORMAL CIRCULATORY DYNAMICS IN AURICULAR FIBRILLATION

There is abundant evidence, both clinical and experimental, that auricular fibrillation produces deleterious effects on the circulation. Stewart and his co-workers[13,14] and Blumgart and Weiss[15,16] showed that the rate of blood flow was slowed in auricular fibrillation by 20 to 68 per cent. The cardiac output was also found decreased.[17,18] Impairment of the circulation could not be ascribed to the increased heart rate for the

cardiac output and rate of blood flow in dogs were found unchanged in regular tachycardia but decreased in auricular fibrillation although the ventricular rates were the same.[14,17] After resumption of normal rhythm the rate of blood flow in dogs returned to normal,[14] and the circulation time in patients decreased by an average of 8 seconds.[15] Landis and his co-workers[19] found a disproportionate rise in central venous pressure after exercise in dogs with auricular fibrillation.

The size of the heart may also be affected by the fibrillating state. Stewart and his co-workers found a decrease in heart size in seven patients after cessation of auricular fibrillation.[18] In one of these, previous digitalization resulted in only a slight decrease in heart size. Stewart and Crawford[20] showed that the size of a dog's heart may increase in auricular fibrillation while it remains unchanged or becomes smaller in regular tachycardia. Levine and Golden[21] inferred that dilatation of the heart in patients with regular tachycardias depends upon duration of the attack, rapidity of the ventricular rate and original health of the heart. Since auricular fibrillation is more prone to cause cardiac enlargement than a rapid regular rhythm of the same rate,[20] it is to be expected that enlargement will occur with slower irregular ventricular rates than in the reported cases of dilatation in regular tachycardias.

A further factor that is often insufficiently appreciated is the effect of effort on the circulatory state when auricular fibrillation is present. Although digitalis may lower the ventricular rate in auricular fibrillation to normal during rest and restore almost normal circulatory dynamics at rest, it does not protect the ventricles from a disproportionate rise in rate with exercise. Blumgart[22] showed that in auricular fibrillation not only was the rise in ventricular rate with exercise greater than in the normal, but that there was a delay in return to normal with rest even in the digitalized patient. In these cases, when normal rhythm was restored by quinidine, there was less acceleration of the ventricles in response to effort.

In the case reports just cited and in some of those to be discussed, it has been noted that treatment with digitalis alone was not adequate to control the symptoms of heart failure. Restoration to normal rhythm following quinidine was found to result in a complete cure in an appreciable number of instances. Such clinical observations are consistent with the experimental data just cited and refute some earlier opinions that the circulatory dynamics in well controlled auricular fibrillation are normal.[23]

*Clinical Material.* This study is based on a review of eighty-four patients with auricular fibrillation who were regarded as having no other evidence of organic heart disease. Fifty-eight of these were seen in private practice and the other twenty-six were observed only at the Peter Bent Brigham Hospital. Of the total there were fifty-three who were intimately observed in the hospital and of these, forty-seven were carefully studied during arrhythmia and after reversion to a normal mechanism. There were seventy-three males and eleven females in the entire series. The average age was fifty years, and the range was from twenty-three to sixty-seven years. Only ten were over sixty years of age and twenty were under forty. Seven of these patients had frank congestive failure and will be reported in detail later. There were seven others who had latent heart failure. Evidence for this was generally reflected in a distinct lowering of the vital capacity of the lungs, a somewhat slower velocity of blood flow (both of which improved after treatment) and dilatation of the heart.

*Symptoms.* Palpitation was the most common chief complaint. Sixty-five of these patients complained of this sensation at one time or another. It is of some interest that there were nineteen instances in which palpitation was absent when fibrillation had occurred. Other primary complaints were weakness (twenty-five cases), breathlessness (twenty-three cases), syncope (thirteen cases)

and nervousness (eight cases). Other major symptoms present in isolated instances were dizziness, ankle edema and chest pain. Anginal pain on effort was present in three patients. Dyspnea and weakness were the most prominent symptoms in the patients with congestive failure.

*Duration.* In this study auricular fibrillation was regarded as permanent if it lasted more than seven days. There were twenty-three patients who had typical transient bouts of auricular fibrillation although in eight of these the arrhythmia had lasted one to seven days when treatment was instituted. These transient episodes covered varying periods of time, in different patients, from one month to ten years. The frequency of recurrences also varied greatly from extremely rare episodes to those that recurred every few weeks or more often. The other sixty-one patients in the series all had permanent auricular fibrillation. Detailed observations concerning the duration of auricular fibrillation were made on those fifty-three patients that were intimately studied in the hospital. The others were treated at home or in various other hospitals, and some were not treated at all or refused treatment. There were thirteen with a duration of eight days to one month, thirty of one to twenty-four months' duration, four of two to three years' duration and six of more than three years, the longest being nine years. Twenty of those with permanent auricular fibrillation had previous transient attacks lasting hours or several days over a period of one to twenty-three years before they were seen. Four of these twenty had previous persistent fibrillation which had been successfully reverted elsewhere by the use of quinidine.

The average duration of auricular fibrillation in the forty-six patients without frank congestive failure was 12.2 months at the time treatment was started, the range being from one month to nine years. The average duration in the seven patients with congestive failure was 3.7 months, and that of seven with latent failure was 11.3 months. It is evident, therefore, that duration of the arrhythmia was not a significant factor in the development of heart failure. It is of interest that in the group of thirteen patients in whom the arrhythmia persisted, either because no treatment was given or because treatment failed, the known average duration of auricular fibrillation was 10.6 years. This does not include an instance in which the irregularity probably was present for forty-four years.

*Associated Conditions.* None of the eighty-four patients had a past history of rheumatic fever or manifested any evidence of rheumatic heart disease. None had any acute infection at the time of examination. Routine urine analyses and blood counts were essentially normal. The blood Wassermann was determined in sixty-three patients. One had well treated asymptomatic syphilis of the central nervous system, two had doubtful reactions without stigmas of lues and the remaining all had negative serologic reactions. Chronic cholecystitis and cholelithiasis were present in four patients. Other conditions, like renal stones, pulmonary emphysema, etc., were rare and not regarded as related to the arrhythmia. The only specific etiologic factors that might be incriminated in the initiation of the fibrillation in a few instances was alcohol and in one instance an excessive amount of privine used in the form of nose drops. In general it appeared that the arrhythmia was not due to infection, toxic influences or associated diseases and had to be regarded as of unknown or of neurogenic origin.

*Heart Murmurs.* Cardiac murmurs were striking by their absence. Only six patients of the entire eighty-four had a faint grade I, and one additional patient had a grade II apical systolic murmur. Three of these murmurs occurred in patients with congestive failure. The murmurs disappeared in these three and in one of the others when the rhythm was regularized. There were no other auscultatory abnormalities except for the arrhythmia.

*Blood Pressure Observations.* The average blood pressure of the entire series was 128/80. The highest was 150/100 during

arrhythmia which fell to 126/90 when the rhythm became regular. Only seven had readings above 145/90. There was no difference between the pressure levels with or without congestive failure. The average blood pressure in eleven patients who had determinations before and after reversion was 145/89 during auricular fibrillation and 133/80 when the rhythm became regular. It is concluded that there was no essential hypertension in this series of patients.

*X-ray Findings.* Seven-foot heart films were made in twenty patients without frank congestive failure during auricular fibrillation and within forty-eight hours after normal rhythm was restored. The interval between the two comparable films was generally only several days. In none of these cases was the heart regarded as significantly enlarged. The average diameter of the heart was 14.4 cm. during arrhythmia and 14.3 cm. after regularization. In three cases the transverse diameter decreased 0.9 cm., 1.4 cm. and 1.0 cm., respectively. In the first there was no evidence of cardiac incompetency during fibrillation. In the second the vital capacity increased 900 cc. when the rhythm became regular, and in the third the circulation time was 26 seconds (decholin) during fibrillation. There was a fourth instance in which no change in heart size was detected directly after reversion although one year later it had decreased 0.8 cm. In this case it required fourteen days to accomplish regularization, during most of which time auricular flutter with a rapid ventricular rate was present. The vital capacity of the lungs rose from 2,400 cc. to 3,700 cc. when the rhythm became regular. Twenty years later this patient was well and had no evidence of heart disease. The latter three of the aforementioned four patients are presumed to have had slight cardiac dilatation and latent congestive failure while they were fibrillating.

Heart films were obtained during and within forty-eight hours after arrhythmia in four of the seven patients with frank congestive failure. The average diameter of the heart in these cases before and after regularization was 17.4 cm. and 15.4 cm., respectively. In one patient, although there was enlargement, no decrease occurred. In two instances the size of the heart became normal and showed a decrease of 3.6 and 4.0 cm. In the fourth patient the heart size decreased 0.9 cm. one day after regularization and there was a further decrease of 2.0 cm. nineteen months later. The only patient with congestive failure who showed no decrease in heart size had had seventy-three attacks of auricular fibrillation (some of them prolonged) in twenty-one years. The irreversible cardiac hypertrophy in this sixty-five year old man was probably the result of long sustained auricular fibrillation. The general contour of the cardiac silhouette in those patients showing enlargement was not remarkable and was regarded as representing for the most part reversible dilatation caused by the arrhythmia. In the larger group without heart failure it is significant that neither the left nor right auricle was enlarged by fluoroscopy.

*Electrocardiographic Observations.* Electrocardiograms were made in all (eighty-four) patients during fibrillation and within one to several days after the auricular fibrillation disappeared. In most cases the tracing was obtained within twenty-four hours. Left axis deviation was present in eighteen patients. None showed right axis deviation. Six patients* showed prolongation of the P-R interval from 0.22 to 0.28 seconds, nine had premature auricular beats and two had both auricular and ventricular premature beats after reversion. In no case were the extrasystoles frequent or troublesome. Three patients without failure showed transient inversion of the T waves in leads II and III, and one with heart failure had transient inversion of the T waves in leads I and II following reversion. It appears that transient prolongation of the P-R interval is not uncommon after cessation of auricular fibrillation. Changes in the T waves have often been observed after reversion of supraventricular or ventricular tachycardia.[24–31] Minor abnormalities in the tracings might

*One reverted spontaneously without any medication.

be confused with those seen in myocardial infarctions but they were not accompanied by any alteration in the QRS complex. Furthermore, the T wave changes may be partly the result of digitalis or quinidine for in most cases one or the other of these two drugs were employed. These T wave changes cannot always be attributed to drug effect for in one of our patients in whom reversion occurred spontaneously without any medication there was transient inversion of the T wave in leads II and III.

*Basal Metabolism Determinations.* There was no clinical evidence of thyrotoxicosis in any case. The basal metabolic rate was determined in fifty-six of these patients. The readings varied from −20 per cent to +10 per cent except for one instance of +20 per cent (during heart failure). The average reading was −7.2 per cent. In a certain number of instances repeat determinations obtained after reversion showed no significant difference. It can safely be assumed that these patients were not suffering from hyperthyroidism.

*Vital Capacity of the Lungs.* For the most part the vital capacity of the lungs was essentially normal in those patients without heart failure and showed only a slight increase after reversion. There were a few exceptions however. Determinations were made in twenty-eight patients during the arrhythmia and one day after the rhythm was regularized. The average figures for the two occasions were 3,448 cc. and 3,700 cc., respectively. There were three instances of abnormally low readings which showed increases of 900, 1,300 and 1,300 cc. when reversion took place. In the group with heart failure the average vital capacity was 2,575 cc. before and 3,725 cc. after reversion. When a marked increase takes place, it is a fair indication that some congestive failure had been present.

*Circulation Time.* The arm-to-tongue circulation time was measured during arrhythmia and again within forty-eight hours after the rhythm became regular in eleven patients without congestive failure. The circulation time with decholin in seven patients varied from 15 to 26 seconds (average 21 seconds) during auricular fibrillation and from 16 to 23 seconds (average 18 seconds) with normal rhythm. The circulation time in the other four patients varied from 19 to 39 seconds (average 29 seconds) with magnesium sulfate during arrhythmia and from 19 to 30 seconds (average 24 seconds) with normal rhythm. Four patients showed significant reductions in circulation times of 6, 6, 8 and 16 seconds, respectively, with normal rhythm. Similar measurements were made during and after arrhythmia in only two patients with heart failure. The rate was 33 and 22 seconds during auricular fibrillation and fell to 14 and 20 seconds, respectively, with normal rhythm. In general it would seem that the velocity of blood flow accelerates somewhat after reversion, particularly in patients who previously had heart failure.

*Venous Pressure.* The venous pressure (method of Lyons, Kennedy and Burwell)[32] was determined in thirteen patients during auricular fibrillation and again within forty-eight hours after the rhythm became regularized. It varied from 60 to 170 mm. $H_2O$, averaging 107 mm. $H_2O$ during the period of auricular fibrillation. When the rhythm was regular, the venous pressure averaged 97 mm. $H_2O$ with a range of 55 to 145 mm. $H_2O$. Only two patients had elevated venous pressures (170 and 160 mm. $H_2O$) during the period of auricular fibrillation; with normal rhythm their venous pressures fell to 140 and 145 mm. $H_2O$, respectively. The venous pressure was 180 and 130 mm. $H_2O$ in two patients with congestive failure during arrhythmia. When the rhythm became regular, it dropped to 150 and 45 mm., respectively. As with other criteria of circulatory dynamics the venous pressure tended to be slightly elevated in those with some failure and returned to normal after treatment.

## TREATMENT

There were sixty-two episodes of auricular fibrillation in this study occurring in fifty-three individuals who received quinidine

therapy. Digitalis was administered to all patients with rapid ventricular rates in order to slow the rate. In only one instance was regularization obtained and that occurred a few hours after 1.2 mg. of digitoxin was given orally. In general the routine of administering quinidine was to give three oral doses daily at four-hour intervals, starting with an initial dose of 0.2 Gm. and increasing each by the amount of 0.1 or 0.2 Gm. In rare instances the patient received four doses a day, and the interval between doses in two patients was two rather than four hours. In our early experience when the three daily doses were identical and increases were made each day rather than in each dose it took longer to obtain reversion. Patients were examined just before each dose of quinidine was administered for if regularization had been obtained by the previous dose the amount of the drug would be decreased to a maintenance dose of 0.2 Gm. two or three times a day rather than increased.

Four patients reverted promptly after the first dose of 0.2 Gm. Four others reverted after the second dose (0.3 Gm.). In thirteen instances regularization occurred after the third dose (0.4 Gm.). Only fourteen patients required doses in excess of 0.7 Gm. In eight the amount had to be gradually increased to single doses of 1.0 to 1.5 Gm. In one case reversion took place after five individual doses of 1.0 Gm. each, and in another after three individual doses of 1.1 Gm. In the final patient regularization did not occur until a dose of 1.5 Gm. was reached. Although the number of patients with congestive failure was not great (seven cases), the dose required for regularization was somewhat larger than in those without heart failure. However, in both groups small doses were adequate in some and very large doses were necessary in others. There were seven failures in the treatment of sixty-two different attacks of fibrillation, i.e., 88.5 per cent successes. In three young men, aged thirty-two, thirty-seven and thirty-nine years, treatment was unsuccessful after individual doses of 0.9, 2.0 and 1.5 Gm., respectively. A fourth was a man sixty years of age who twice before responded satisfactorily to quinidine therapy but finally was refractory even to doses of 1.0 and 1.2 Gm. In a fifth case treatment had to be discontinued after a dose of 0.5 Gm. because of marked nausea and ringing in the ears. Another forty-seven year old man developed auricular flutter and failed to become regular despite a dose of 1.0 Gm. (Case VII.) The last patient was a sixty-seven year old man who responded favorably to quinidine many times in the past but finally failed to revert on increasing doses up to 1.5 Gm. This patient was even given 1.2 Gm. intravenously without success. A short time later regularization did occur at another hospital but the dosage employed is not known. (Case V.) In all cases in which the arrhythmia persisted after quinidine therapy a proper maintenance dose of digitalis was given. The previous duration of the irregularity did not have any significant influence upon the ease with which normal rhythm could be restored or the dose of quinidine required. It is evident that as a group these patients have a high incidence of favorable response to quinidine (88.5 per cent) and that only small or moderate doses were required in most cases. It is obvious, however, that some of the most satisfactory results were obtained only when very large doses were employed. This experience is in striking contrast to the results obtained in the treatment of mitral stenosis and auricular fibrillation. In that condition regularization following quinidine cannot be expected to occur in more than one-third to one-half of the cases.

*Toxic Reactions and Complications.* Worrisome toxic reactions with quinidine were very uncommon in this group of patients. With the large doses that were used in some of the patients, there was often a feeling of slight nausea, weakness and buzzing in the ears. These symptoms did not interfere with our therapy nor did they inhibit us from continuing quinidine if it seemed indicated. There was one patient that went into shock after receiving five 1 Gm. doses

of the drug. In fact, it seemed as if his heart had actually stopped. The patient had a convulsion but normal rhythm was quickly resumed with complete recovery. (Case II.) One woman, fifty-five years old, had a mild left hemiparesis forty-eight hours after resumption of normal rhythm. Complete recovery took place four days later. A diagnosis of questionable embolism was made. A third patient had a transient erythematous macular rash forty-eight hours after the last dose of quinidine. Auricular flutter developed in ten patients during quinidine therapy. In seven of these patients normal rhythm was eventually resumed and in three auricular fibrillation returned and persisted. It is striking that serious complications were practically absent so that quinidine therapy can be regarded as a safe procedure in the group of patients with auricular fibrillation who had no significant heart disease.

### PROGNOSIS

The prognosis in this group was quite good. There were seventy-one patients in whom adequate follow-up information was available. Of the fifty-three intimately studied in the hospital only six subsequently died. One patient had a recurrence of auricular fibrillation after maintaining a regular rhythm for three years. No attempt at re-regularization was made. One and one-half years later he developed angina pectoris and died six months after this at the age of fifty-five. (Case III.) Two others relapsed into auricular fibrillation and died of an unknown cause one and two years later at the ages of sixty-nine and sixty-one years, respectively, having first manifested gross irregularity six and four years before death. Two patients died of cancer at the age of sixty and sixty-three, the first twelve and one-half years and the other six months after reversion to regular rhythm. The sixth died as the result of an automobile accident one month after quinidine therapy.

In addition, there were five deaths among the thirty-one other patients. One was shot three years after the onset of arrhythmia. Another man died at the age of forty-one from angina pectoris which he had for six months, seventeen years after the onset of auricular fibrillation. A third died of cerebral hemorrhage eight years after fibrillation was first noted. Autopsy did not reveal any embolism. The other two patients died of cerebral emboli at the ages of fifty-two and sixty after thirty-one years and five and one-half years, respectively, of chronic auricular fibrillation. Considering the large number of patients, especially males, involved in this study it is not surprising that there have been a small number of cardiovascular fatalities such as those due to coronary or cerebral vascular disease. This would necessarily be true of any group of adults followed well into the second half of life. The one cardiac complication that might be directly related to the presence of auricular fibrillation would be emboli coming from auricular mural thrombi. We have no case of this sort that has been confirmed postmortem. The two instances in which the clinical diagnosis of cerebral embolism was made afford presumptive evidence that thrombi may develop in the left auricle in these cases. If this is so, the evidence presented indicates that it must be a rare phenomenon.

The average duration of life among the sixty living patients is 10.0 years from the beginning of the cardiac arrhythmia. The average age of these patients when last heard from was 56.0 years. During this period of observation there was no known instance of thyrotoxicosis. One patient developed coronary thrombosis at the age of fifty-two from which he recovered. This illness occurred four years after a recurrence of persistent auricular fibrillation. He was doing well although still fibrillating two years later. Another patient began to show evidence of congestive failure while in persistent fibrillation but responded to cardiac therapy and is still able to do a moderate amount of work as a farmer two years later. A final patient (Case VII) had hemiplegia two years after the onset of

auricular fibrillation which did not respond to quinidine. The striking feature is the absence of either heart failure or any other significant cardiac disability except palpitation in most of these patients.

### DURATION OF REGULAR RHYTHM

Among the patients observed intimately in the hospital there were forty-seven in whom regularization was obtained. Adequate follow-up information was available in forty-three. Twenty-five of them were fifty years or older and eighteen were under fifty years. Nineteen of the older group relapsed into auricular fibrillation; nine did so within one year, but the average duration of normal rhythm before relapse in this group was twenty-one months. In the younger group only five of eighteen patients relapsed, and the average duration of normal rhythm before relapse was 61.4 months. Only one of this group relapsed within one year. The average duration of regular rhythm in the entire group that did relapse was 26.9 months. It is evident from this analysis that the duration of regular rhythm is much longer in the younger than in the older patients.

Another factor that seemed to influence the duration of regular rhythm was the length of time auricular fibrillation had previously been present. In the group in which the irregularity persisted for over one year regularization lasted an average period of 15.6 months. When fibrillation had been present less than one year, the subsequent period of regular rhythm was 35.1 months. These figures only pertain to those who reverted to the irregularity. There were nineteen patients who maintained a regular rhythm throughout the period of observation. Only two of them had had auricular fibrillation for more than one year and all but five were under fifty years of age. It is of interest that one patient has maintained a regular rhythm for twenty-one years since reversion. It follows, therefore, that the shorter the period of irregularity the longer the period of regular rhythm.

### COMMENT

All the factors which lead to heart failure in patients with auricular fibrillation but without evidence of organic heart disease are not known. The duration of auricular fibrillation did not appear to be the determining factor. Friedlander and Levine[5] reported four such cases of permanent auricular fibrillation of nine and thirty-one years' duration in which no evidence of heart failure was present. One of these patients has had this gross arrhythmia now for twenty-seven years. It started at the age of twenty-two, and for the following fifteen years he received no cardiac medication whatever although the ventricular rate was moderately rapid. He always refused to try quinidine. In 1935 during the course of lobar pneumonia the ventricular rate rose to 185. He was then digitalized and has taken a maintenance dose of 0.1 Gm. of digitalis leaf daily ever since. There has never been any evidence of heart failure. This patient is able to do hard work without difficulty at the present time. During the past twenty years the vital capacity of the lungs decreased from 4,300 cc. to 3,600 cc. There were three other patients in this present study who were known to have had persistent auricular fibrillation for fifteen years without complications, and another instance in which it was judged from the history that the arrhythmia had persisted for forty-four years without producing cardiac failure.

It is of further interest that frank congestive failure did not occur in any patient with auricular fibrillation of more than one year's duration, but there were two instances in which latent congestive failure was present when the irregularity lasted three years. In all seven instances of frank failure and in five of the seven cases of latent heart failure the irregularity lasted only weeks or months. It would appear that if heart failure is to develop it does so comparatively soon after the irregularity first appears if it persists.

The actual ventricular rate seems to have a definite influence on the development of heart failure in these cases. The average ventricular rate before digitalis therapy in those with frank failure was 146 (ranging from 122 to 170), in those with latent failure 119 (ranging from 100 to 134) and in those without failure 100 (ranging from 72 to 160). Only two of the latter group had heart rates over 118.

It is impossible to predict how long normal rhythm will persist in any given patient. The ease with which the patient reverted to normal rhythm on quinidine was no index to the duration of regular rhythm. Fifty per cent of those who responded favorably after one to three doses of quinidine went back into auricular fibrillation within six months. In contrast, one patient who required three doses of 1.1 Gm. each had no recurrence of arrhythmia in the subsequent twenty-one years.

In appraising the value of regularization of the heart by use of quinidine one naturally would have to consider the risk of the procedure, duration of the regular rhythm once it had been obtained and improvement in the general health of the patient. In this group of cases under consideration there were no untoward results. One may conclude that the risk was negligible. The duration of regular rhythm was sufficiently long to make one believe that therapy was worth while. The average duration of normal rhythm will obviously become longer and longer because many patients are still continuing with a normal heart rhythm for years. Finally, the group that had congestive failure was obviously helped tremendously as they were restored to good health. The same was true to a less dramatic degree in those who had latent failure. The experience with the latter two groups of cases lead us to the opinion that development of heart failure was prevented by regularization of the rhythm in some of the other patients who were well compensated and essentially asymptomatic.

A certain number of patients are encountered in practice who have auricular fibrillation and cardiac enlargement without apparent cause. These are often diagnosed as "heart disease of unknown etiology" or as "chronic myocarditis." Perhaps if the blood pressure is slightly elevated the case is designated as hypertensive heart disease. In time, irreversible cardiac enlargement and chronic congestive failure lead to death. We believe that many such cases originally were instances of auricular fibrillation without significant heart disease. Our six cases of frank congestive failure which were reverted to normal rhythm would undoubtedly have remained in chronic congestive failure on digitalis therapy and considered as examples of "chronic myocarditis." Restoration of normal rhythm abolished the congestive failure and revealed an essentially normal heart. The seven patients with latent congestive failure also illustrate the same sequence. Progressive cardiac enlargement and congestive failure would probably have developed and become irreversible if the auricular fibrillation had been allowed to persist. It is obvious that auricular fibrillation cannot be assumed to be due to organic heart disease. Such an attitude might make the physician fearful of using quinidine and condemn these patients to chronic invalidism and eventually to a cardiac death when the condition might have been prevented early in its progress or corrected even after it had become fairly well advanced.

## SUMMARY AND CONCLUSIONS

1. Eighty-four patients with auricular fibrillation of unknown etiology who had no evidence of organic heart disease were studied. Sixty-one had permanent fibrillation and twenty-three had transient fibrillation. Eighty-seven per cent of these were males. The average age was fifty years, ranging from twenty-three to sixty-seven years. The average blood pressure was 128/80. The average basal metabolic rate was −7.2 per cent.

2. Forty-seven patients were studied carefully before and after reversion of the

arrhythmia with quinidine. Six had marked congestive failure. A seventh patient who did not respond to quinidine also had congestive failure. Seven others had latent congestive failure.

3. The most common symptom of those without failure was palpitation. In the group with failure the customary features of dyspnea, orthopnea and an enlarged liver were present.

4. The transverse diameter of the heart averaged 14.4 cm. during fibrillation and 14.3 cm. after reversion in twenty patients without frank failure. The transverse diameter in four cases of congestive failure averaged 17.4 cm. during and 15.4 cm. after auricular fibrillation.

5. Six patients had slight prolongation of the P-R interval after reversion. One of these reverted spontaneously without any medication. Four patients showed transient inversion of T waves after reversion, one of which reverted spontaneously without any medication.

6. The vital capacity of the lungs averaged 3,448 cc. in twenty-eight patients without failure during auricular fibrillation and 3,700 cc. after reversion. In the group with failure the vital capacity increased from 2,575 to 3,725 cc.

7. The arm-to-tongue circulation time in eleven patients without failure averaged 24 seconds during auricular fibrillation and 20 seconds after regularization.

8. The venous pressure averaged 107 mm. $H_2O$ in thirteen patients without failure during auricular fibrillation and 97 mm. $H_2O$ after reversion.

9. Regularization following quinidine occurred in 88.5 per cent of the patients and there were no untoward complications. In those that did relapse the normal rhythm persisted on the average for 26.9 months. The average duration of regular rhythm in patients under fifty years who relapsed was 61.4 months; in those over fifty it was twenty-one months. Nineteen patients have not relapsed and still have regular rhythm after two months to twenty-one years. This maintenance of regular rhythm is much longer than in patients with organic heart disease who were reverted with quinidine.

10. In the group showing advanced congestive heart failure, dramatic therapeutic responses were obtained, all symptoms and signs of heart failure disappearing after regularization.

11. It is concluded that auricular fibrillation *per se* may produce cardiac dilatation and progressive congestive failure in patients with otherwise normal hearts. This is a truly reversible type of heart failure.

12. There is reason to believe that a considerable number of patients with auricular fibrillation, cardiac enlargement and congestive failure (that eventually becomes irreversible) have little or no organic heart disease. We are also of the opinion that regularization of the rhythm with quinidine in the early stages may prevent progressive heart failure and in the latter stages may even be curative.

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*Case Reports will be included in the reprint.*

# Function of the Kidney and Metabolic Changes in Cardiac Failure*

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THE purpose of this paper is to present and discuss some studies designed to describe the functional alterations of the kidney in cardiac failure.

It has long been known that in congestive failure with edema the excretion of sodium chloride is impaired and that the kidney function, as measured by less precise clinical tests, is diminished. During the years preceding the application of the more precise tests of renal function the kidney was assigned a secondary role in the pathogenesis of edema. According to Starling's conceptions, an increased extravasation of fluid through the peripheral capillary membrane due to increased venous back pressure from the failing heart was considered the primary cause of edema.[1] However, in his lectures in 1908 Starling surmised that the failing heart with low output would lead to peripheral splanchnic constriction and that the reduced flow to the kidney would lessen the output of fluid.

In recent years, since the application of clearance methods of determining renal blood flow and glomerular filtration rate, the kidney has been assigned a primary role in the accumulation of edema. The renal retention of salt was ascribed by Stead, Warren and Merrill to the effects of diminished blood supply to the kidney from the failing heart.[2] This was designated "forward failure" to the kidney and was considered to be the primary factor in edema formation, in contrast to the factors of backward pressure in the peripheral capillary or to the effect of venous pressure upon the kidney itself.

In 1942 the first extensive studies correlating cardiac output with changes in the renal circulation and venous pressure were made by Seymour, Pritchard, Longley and Hayman.[3] They found reduction in renal blood flow and glomerular filtration rate with a lowered cardiac output. After cardiac compensation, with a rise in cardiac output, the renal blood flow increased more than the glomerular filtration rate. They attributed the renal circulatory pattern during failure to the effect of high venous pressure upon the kidney. Later in 1944 Merrill confirmed these findings but noted that the diminution in renal blood flow correlated well with the diminution in cardiac output but had no correlation with the height of venous pressure.[4] Merrill concluded that increased venous pressure was not the cause of the decreased renal blood flow with a relatively high glomerular filtration rate, but that the renal circulatory pattern was the result of inadequate output of the failing heart, causing constriction of the efferent glomerular arterioles which would tend to maintain the intraglomerular pressure.

This pattern of the renal circulation in cardiac failure is now well established. There may be constriction of the afferent glomerular arteriole also but there is relatively more of the efferent component. It is apparent that reduced blood flow due to

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constriction of the efferent arteriole of the glomerulus tends to maintain or increase the pressure in the glomerular capillaries even though it offers resistance to the total blood flow. That this type of adjustment in the intrarenal circulation might take place was suspected by Starling and has been described extensively by Homer Smith and other workers.

The question then arises, how does this circulatory pattern bring about the reduction in excretion of sodium and chloride which are the main constituents of edema fluid? Merrill and Stead, and lately Leiter and Mokotoff, have elaborated further upon the relationship of the circulation to sodium retention by the kidney.[5] They believe that the primary cause of the renal retention of sodium is the diminished glomerular filtration rate. They reason that the decrease in the amount of fluid filtered by the glomeruli, and hence of sodium presented to the tubules, causes the low output in the urine. It was suggested by Merrill that when the glomerular filtration rate falls below a "critical level" of about 70 cc./min., retention of sodium is marked because almost all of the filtered sodium is reabsorbed by the tubules.

Thus it has been shown that the renal blood flow and glomerular filtration rate are reduced in cardiac failure and it has been postulated that the primary change in the kidney responsible for sodium retention is decrease in the glomerular filtration rate.

Our studies were made to describe the mechanism of salt retention by the kidney by correlating the changes in renal function with the clinical and metabolic condition of the patient, also to determine some of the factors causing salt retention by a study of the effect of stress and drugs upon the kidney in normal subjects and patients with cardiac failure. In the study of the correlation of renal function with the clinical and metabolic condition of the patient we have followed the principle of making intensive study of a few patients throughout the course of their failure rather than a few observations on many patients at different stages of failure. If the theory that diminished filtration rate causes salt retention is correct, one might expect some correlation between the over-all balance of sodium and the level of glomerular filtration rate. Another principle which we have followed is that of accurately determining the body balance of electrolytes since the kidney is primarily responsible for the maintenance of this balance. If some function of the kidney is to be held responsible for the amount of edema, it seems inescapable that accurate proof of gain or loss of the extracellular fluid ions, sodium and chloride, must simultaneously be provided. Furthermore, since we suspected that changes in the composition of tissue cells might result from congestive heart failure we have determined the metabolic balances of nitrogen and of the main intracellular cation, potassium.

The first patient studied was a thirty-seven year old colored woman with marked congestive failure secondary to rheumatic mitral and aortic valvular deformities. There was no clinical evidence of active rheumatic fever. When admitted to the hospital she was markedly orthopneic and dyspneic while at rest in bed; there was distention of the neck veins and peripheral edema.

Figure 1 shows weight (solid dots) and venous pressure (hollow dots) with the periodic determination of glomerular filtration rate (GFR), renal plasma flow (RPF) and the filtration fraction (FF) during the course of four months. Each point concerning renal function represents an average of from three to six determinations during two to three hours on that day. During the first forty days weight loss, fall in venous pressure and symptomatic improvement were associated with a rise in renal plasma flow and fall in filtration fraction to normal. There was no significant change in the glomerular filtration rate. Thereafter the patient was at home and the circulatory status deteriorated again. She returned to the dispensary and was observed again to exhibit increased weight and venous pressure with markedly reduced renal plasma

flow but with the same glomerular filtration rate.

The glomerular filtration rate was quite constant and within normal limits for this patient throughout the entire period of observation. Her normal glomerular filtration rate according to the standards of Homer Smith would be 100 cc./min. The range was 85 to 115 cc./min.

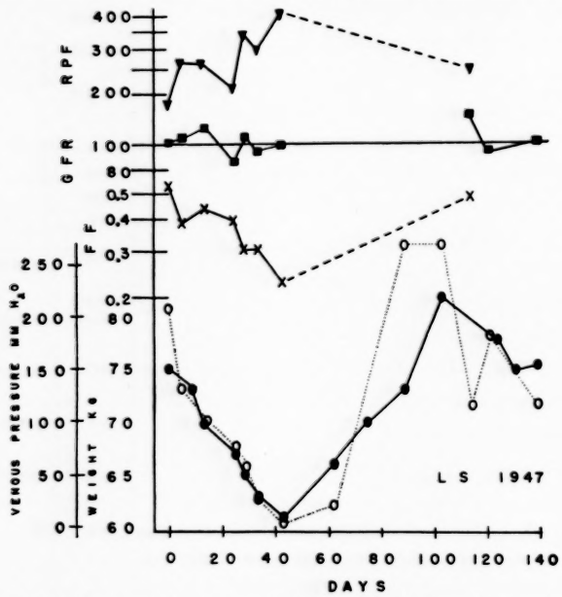


FIG. 1. Summary of the determinations of renal plasma flow (RPF), glomerular filtration rate (GFR), filtration fraction (FF), body weight (solid dots) and peripheral venous pressure (open circles) in patient L. S.

During the period of weight loss metabolic studies were performed on this patient. No medication except a maintenance dose of digitalis was given. (Fig. 2.) On the top of the chart are the periodic determinations of glomerular filtration rate ($C_{In}$), renal plasma flow ($C_{PACA}$) and filtration fraction (FF) over the twenty-four days of observation, with weight (WT) and venous pressure (VP). Below are the daily balance boxes for sodium, chloride, potassium and nitrogen determined by chemical analyses of the patient's dietary intake and urinary and stool output. The darkened areas when above the line represent negative balance or loss; when below the zero line, positive balance or retention. The distance from the bottom of the daily box up to the zero line represents the intake.

Loss of sodium and chloride were parallel to the drop in weight and venous pressure. At first the intake of sodium chloride was low (2 Gm. of sodium chloride); later the intake was raised by an additional 5 Gm. of sodium chloride. The increased intake had very little effect on the general course of sodium chloride balance, the kidney rapidly excreting the extra salt. All these changes in sodium and chloride balance and total output took place without any significant variation in the glomerular filtration rate.

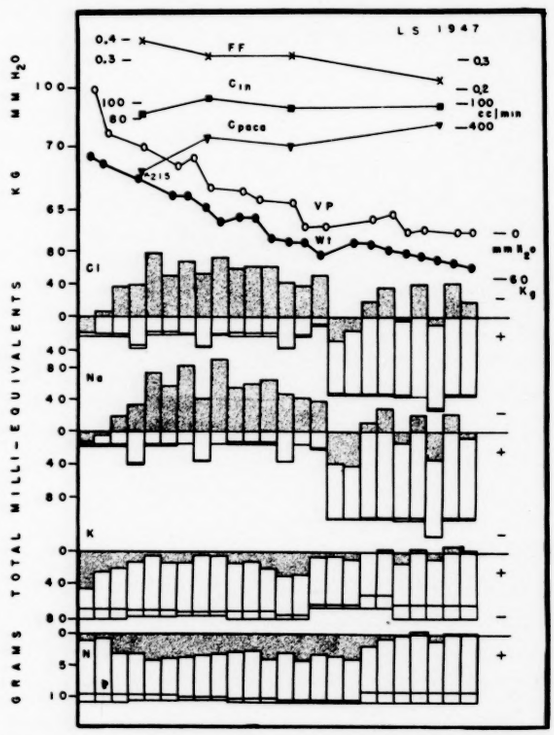


FIG. 2. The renal function determinations, venous pressure (VP), body weight (WT) and daily metabolic balance boxes for chloride, sodium, potassium and nitrogen in patient L. S. over the twenty-four days covering the period represented by days 20 to 44 in Figure 1. Nitrogen is in Grams; electrolytes in milli-equivalents. FF is filtration fraction, $C_{in}$ is clearance of inulin or the glomerular filtration rate and $C_{paca}$ is clearance of para-acetyl-aminohippuric acid and is a measure of renal plasma flow. The shaded areas in the balance boxes when above the zero line represent negative balance or loss, and when below the zero line, positive balance or gain. The distance from the bottom of a box to the top is the total daily output and the distance from the bottom of the box to the zero line is the intake. The small section at the bottom of each box is the daily output in the stool. The remainder of the output is in the urine.

We conclude from these observations during recovery from congestive failure that the excretion of sodium chloride is not necessarily correlated with changes in glomerular filtration rate. Furthermore, a normal glomerular filtration rate can be maintained during congestive failure.

Of interest is the marked change in the balances of potassium and nitrogen. Large amounts of nitrogen (representing 20 to 30 Gm. of protein a day) were retained for two weeks. Furthermore, the retention of potassium was more than could be accounted for on the basis of the ratio of the amount of potassium to nitrogen in body cells.[6] There are two possible explanations for the protein storage. First, it may represent repletion of stores lost because of previous dietary inadequacy; second, it may represent repair of injury to body cells. Injury to cells might occur directly from circulatory insufficiency or by a catabolic reaction due to adrenal cortical activity. The retention of extra potassium might also be a replacement for sodium which had entered tissue cells during failure. These speculations concerning the significance of potassium and nitrogen retention obviously require further investigation.

The second patient was a thirty year old man with a history of rheumatic heart disease. He had dyspnea with minimal cyanosis on slight exertion. He had minimal but definite edema of the feet and a venous pressure of 160 mm. of water. His heart was enlarged to the left and right and the electrocardiogram revealed auricular fibrillation. Enlargement of the left auricle and calcification of the mitral valves were demonstrated by x-ray. He had been taking digitoxin, 0.1 mg. a day, for several months and this was continued with no other medication.

On the top of Figure 3, which covers one month, it is to be observed that the glomerular filtration rate was 70 to 80 cc./min., which is 50 per cent of the expected normal value for this patient since he was a large man. The renal plasma flow was 180 to 220 cc./min., which is about 30 per cent of normal, resulting in an elevated filtration fraction of 0.40. Throughout the period of balance study no significant change in these values occurred. The initial loss of weight was accompanied by a fall in venous pressure from 160 mm. to normal and there

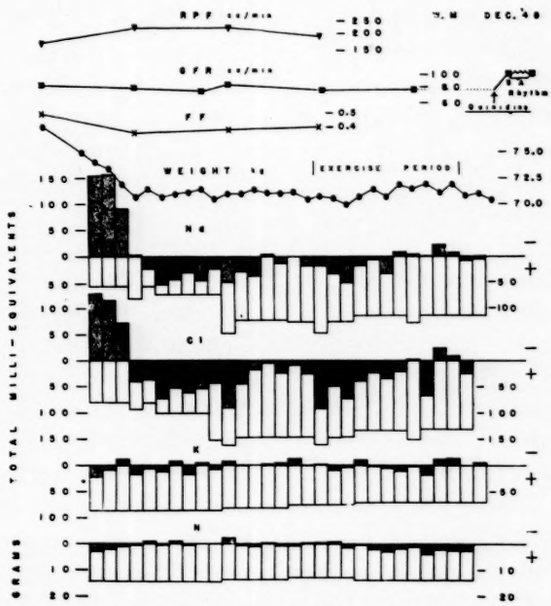


FIG. 3. The renal function determinations, body weight and daily metabolic balance boxes of sodium, chloride, potassium and nitrogen in patient W. M. After the metabolic studies were completed the patient's auricular fibrillation was converted to sinus rhythm by quinidine administration. This was followed by a rise in glomerular filtration rate to 100 cc./min., accompanied by no further weight loss. Method of construction of the balance chart same as in Figure 2.

was marked negative balance of sodium and chloride. Following this there was retention of sodium and chloride for several days. The total amount retained during this period was nearly equal to that lost previously. However, no change in weight accompanied this retention. During this phase the intake was changed from 3 Gm. of sodium chloride to 7 Gm. The extra salt was promptly excreted with no alteration in the balance pattern. Later the patient was allowed up and given daily exercise which was associated with some further sodium chloride retention. No significant gain or loss of potassium or nitrogen occurred in this patient.

We conclude from this study that a glomerular filtration rate 50 per cent of normal and a renal plasma flow diminished to one-third normal did not prevent loss of edema and superfluous body sodium, nor was there any correlation between either glomerular filtration rate or renal plasma flow and sodium chloride balance. This patient had persistent renal ischemia throughout the observation period and was able to excrete stored body sodium as well as sodium added to his intake. The renal blood flow did not increase with compensation as in the first patient.

It is of some incidental interest that after completion of the balance study the auricular fibrillation was converted to regular sinus rhythm by quinidine administration. This was accompanied by a definite rise in glomerular filtration rate which was probably a reflection of a more efficient cardiac mechanism producing increased output.

This patient showed no disturbance in potassium or nitrogen balance. It is difficult at this stage of our knowledge to speculate on the reasons for the difference between the behavior of potassium and nitrogen in the two patients. The latter patient had only mild congestion and edema and at no time was in as severe congestive failure as was the first patient. Another feature which is difficult to explain is the lack of weight gain associated with a significantly large retention of sodium and chloride. One wonders if a shift in body water occurred so that a loss in cell water balanced a gain in extracellular water. In other words, might there be a shift of water from cells to extracellular fluid which would require a gain in sodium and chloride without over-all gain in weight?

In general, from these case studies and others not reported here, we have found no simple correlation between the course of body sodium chloride balance and the renal circulatory pattern during recovery from congestive cardiac failure and edema. It is apparent that other factors must play a decisive role in governing the excretion of salt by the kidney. The idea that a diminution in glomerular filtration rate is the primary reason for retention overlooks the possibility of metabolic or humoral influences upon the renal tubular cells which are responsible for the reabsorption of most of the glomerular filtrate. These metabolic changes might be initiated by the effects of inadequate circulation to other parts of the body. It is certainly not unreasonable to suspect that antidiuretic and salt-retaining humoral substances may be liberated and increase the renal tubular reabsorption of salt. Furthermore, very little or nothing is known about the influence of the renal nerves upon renal cell activity although nerve endings around the renal tubules were demonstrated by Berkley in 1893.[7] Marshall demonstrated increased excretion of water and chloride by the denervated kidneys of dogs.[8] These experiments have recently been repeated by Kriss, Futcher and Goldman.[9] I know of no proof of the nervous control of renal electrolyte excretion since the advent of modern methods for studying renal function.

Thus the renal tubular cells are exposed to many possible influences besides alterations in the amount of glomerular filtrate presented to them. Reduction in the amount of glomerular filtrate presented to the renal tubules may occur in cardiac failure but apparently other factors governing renal tubular activity are as important. The renal tubular cells are ultimately responsible for the regulation of output by selective reabsorption, allowing a small percentage of the filtered substances to escape into the urine.

Before concluding, one type of experiment should be considered which demonstrates a specific influence of exercise on sodium and chloride excretion and may represent in part the renal mechanism responsible for the edema in cardiac failure. The most common stress in our daily lives is exercise, standing and walking. In a patient with congestive failure it is known from clinical observation that ordinary daily exercise may lead to edema. The effect of mild exercise on normal people and on patients with cardiac failure has been investigated in

order to gain some insight into alterations in the renal mechanism which may occur.

The data in Figure 4 represent the effect of walking the length of the ward corridor ten times (200 yards) in thirty minutes on the renal circulation and electrolyte excretion in a patient with congestive cardiac failure. The patient was a fifty year old man who was admitted to the ward with congestive failure following an episode of substernal pain six weeks previously. He showed dyspnea on exertion, elevated venous pressure, an enlarged heart with normal rhythm and normal blood pressure. There was marked edema of the legs and some over the sacrum. The electrocardiogram was interpreted as showing evidence of an old anterior myocardial infarction. As seen on the lower portion of the illustration the glomerular filtration rate ($C_{In}$ and $C_{Cr}$) was 80–90 cc./min. or about two-thirds normal, the renal plasma flow ($C_{PACA}$) 200 cc./min. or one-third normal with a filtration fraction of 0.3 to 0.4. There was no consistent change in filtration rate or renal plasma flow during the exercise. The pattern was that of renal ischemia with evidence of efferent glomerular arteriolar constriction producing a high filtration fraction. Above are the curves for the excretion of water and the electrolytes, potassium, phosphate, sodium and chloride. Since one is particularly interested in the reaction of the renal tubular cells to the glomerular filtrate, the urinary output of these substances has been expressed as the per cent of the glomerular filtrate which is excreted. In other words, a fall in the percentage excreted means that the tubular cells have reabsorbed a higher fraction of the amount of the substance presented to them by the glomeruli. Furthermore, the chart is so constructed that one can immediately detect a selective change in one electrolyte with respect to another. If the tubules are changing their percentage reabsorption in an unselective manner, the lines would all be parallel. Deviation of one line from another represents a selective

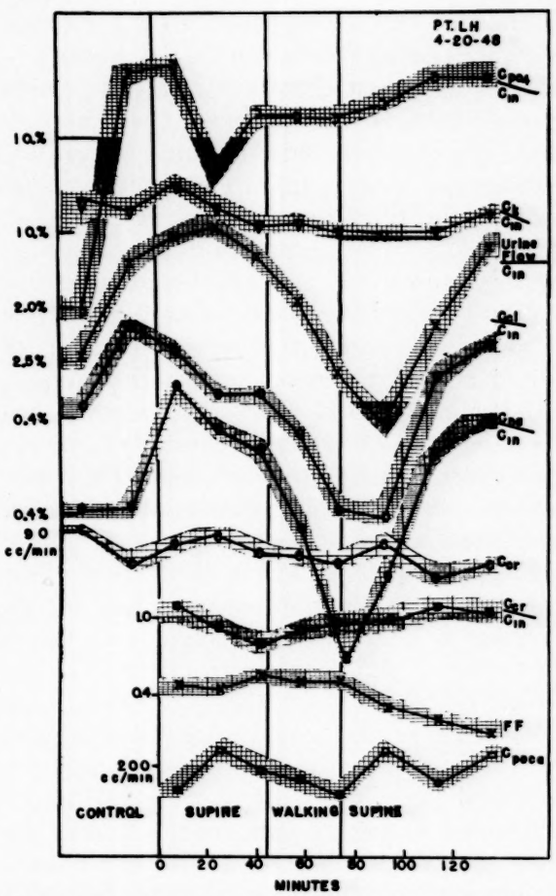


FIG. 4. The changes in renal function and electrolyte excretion during and following the injection of test materials (called "control" and first "supine" rest periods), during exercise (walking) and during a recovery rest period (second "supine" period). $C_{PO_4}$ is plasma clearance of phosphate; $C_k$ is clearance of potassium; $C_{Cl}$ is clearance of chloride; $C_{Na}$ is clearance of sodium; $C_{cr}$ is clearance of creatinine; FF is filtration fraction; $C_{paca}$ is clearance of para-acetyl-aminohippuric acid and is a measure of renal plasma flow. Glomerular filtration rate was determined by both the clearance of inulin ($C_{in}$) and creatinine. The patient L. H. had congestive cardiac failure with edema at the time of observations. In this patient specific sodium and chloride retention occurred without significant changes in the glomerular filtration rate or renal plasma flow measurements. The excretion of potassium and phosphate was unaffected by the exercise and did not parallel the marked fall in sodium and chloride excretion. This pattern of electrolyte excretion is typical of that seen in the patient with cardiac failure. Frequently a fall in glomerular filtration rate is observed also. This type of response to exercise can be observed in normal subjects, with or without a measurable drop in glomerular filtration rate. In the cardiac subject the retention of sodium chloride is much more marked than would be observed generally with the same amount of mild exercise in a normal subject.

change in exact proportion to the relative distances between the lines on the chart.

It is apparent that a dramatic selective change in the excretion of sodium, chloride and water occurred without significant change in potassium, phosphate or the glomerular filtration rate during exercise. The change in sodium is ten-fold, and return to the pre-exercise values occurs after rest.

The investigator must be careful in this type of experiment to observe the effects of the injected substances on renal function. During the period marked "control" are recorded the changes in electrolyte excretion caused by the injection during the first ten minutes of the test substances, inulin and para-acetylaminohippuric acid. These changes are recorded in order to be certain that a fairly steady state is reached before exercise is begun. It is known from other experiments that the electrolyte excretions would be parallel and nearly constant if no exercise were performed after these adjustments took place. These observations serve to emphasize that the interpretation of electrolyte excretion patterns must be made with the closest scrutiny of the test conditions and the effect of substances injected.

It is concluded, then, that inadequate output of the failing heart may produce complicated and profound metabolic effects on peripheral tissues as well as on the functions of the kidney. The patient must be studied not only at rest but also under the stresses of daily activity. Only then can one obtain an integrated picture of the many inter-related factors involved in the production and retrogression of congestion and edema. It has been noted that ischemia of the kidney occurs presumably as a result of inadequate cardiac output. This may cause some retention of sodium and chloride by diminishing glomerular filtration rate. However, the ultimate responsibility for retention rests with the specific selective mechanisms of the renal tubular cells whose reabsorptive activity must be sensitive to factors other than the reduction in the amount of fluid presented to them by the diminished circulation. The effects of posture, exercise, humoral substances and the renal nerves have yet to be adequately determined, and the nature of the metabolic injury to other tissues is a relatively unexplored phase of the problem.

Many people have contributed to this work which began with a study of methods of determining renal function with Dr. James Bordley III and Dr. Louis Alpert in 1942. In carrying out the metabolic balance studies we have had the advice and cooperation of Dr. John Eager Howard and the technical assistance of Mr. Harry Eisenberg and Miss Dorothy Wagner. The dietary regulation and calculations were carried out by Miss Janette Carlsen, Mrs. Lucille Opie and Mrs. Barbara Crozier. The chief contribution of work in the laboratory has been made by Miss Marion Birmingham and Miss Margot Robinson. We have also had the advice of Drs. E. K. Marshall, Kenneth Blanchard and E. Cowles Andrus.

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# Tricuspid Stenosis—A Simple Diagnostic Sign*

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FOR a long time the occurrence of tricuspid valvular disease had been considered rare and its clinical recognition almost impossible. Studies[1–8] during the past ten years, however, have added much to our knowledge of this valvular lesion. It has been shown that the condition is not so rare and that its clinical diagnosis can often be made. Nevertheless the definitive diagnosis of a tricuspid lesion, and specifically of tricuspid stenosis, is still difficult at the bedside. The following observations are recorded to describe a new clinical sign which is simple to elicit and indicative if not pathognomonic of tricuspid stenosis.

## CASE REPORT

P. S., a forty-four year old white man, dress operator, was admitted to the medical service of Beth Israel Hospital. There was no history of polyarthritis or chorea but he was known to have had a cardiac condition for twenty-five years. This was asymptomatic for twenty-two years during which time he worked regularly. During the three and a half years prior to admission he attended the cardiac clinic of the hospital because of dyspnea, orthopnea and slight cough, some lack of his usual endurance and weakness. He also had been having attacks of precordial distress, sensations of internal pressure of moderate severity, lasting ten to twenty minutes each two to five times a week; these were not especially related to exertion but caused him to stop work temporarily. For two to three months before admission these symptoms grew worse and he had frequent attacks of paroxysmal nocturnal dyspnea. His sputum was often blood-tinged.

Physical examination revealed him to be well developed and well nourished, slightly dyspneic and slightly cyanotic. His temperature was normal. The sclerae were not icteric. The heart percussed enlarged to the left and downward. The apical impulse was felt 12 cm. from the midline in the fifth intercostal space. A systolic thrill was felt over the base especially over the aortic area. The following murmurs were heard: at the apex a loud, rough systolic and a less rough diastolic and presystolic; at the base a loud, rough systolic and a faint, blowing, early diastolic, loudest over the aortic area; at the tricuspid area (just to the right of the lower sternum) a rough, moderately loud diastolic murmur; a thrill was not felt over this area. $A_2$ equalled $P_2$ and was not accentuated. The rate was 80 to 90 per minute and regular. The radial pulses were small. The blood pressure was 135/90. With the patient in the sitting position the neck veins were distended and were seen to have fairly marked pulsations. When these pulsations, felt over the right carotid and jugular area, were correlated with the heart sounds they did not seem to be systolic in time. With the index finger of the left hand placed over the right jugular pulse near the base of the neck and the index finger of the right hand placed in the suprasternal notch, the impulses felt under both hands were quite forceful but not synchronous; the jugular came just before the one in the suprasternal notch. The latter was systolic and due to the pulsation of the dilated aorta and innominate artery; the former, venous and presystolic, apparently was produced by the contracting hypertrophied right atrium.

Over the lung bases, right and left, a few rales were heard on inspiration. The respiratory rate was 32 per minute. The liver was enlarged to three fingerbreadths below the costal margin and gave an impulse synchronous with the heart beat. The spleen was not palpable. There

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was slight pretibial edema; no clubbing was present.

Laboratory data were as follows: The urine showed 1+ albumin. The hemoglobin was 15.0 Gm. (per cent); erythrocytes 5,630,000 per c.mm. of blood. The blood Wassermann test was negative. The erythrocyte sedimentation rate was 5 mm. in forty-five minutes. N.P.N. of the blood was 39 mg. per cent. The venous pressure was equal to 17 cm. of water. The patient was not cooperative enough accurately to record the circulation time.

The teleroentgenogram revealed the cardiac silhouette to be markedly enlarged and fluoroscopy disclosed enlargement of all chambers, dilatation of the aorta and calcification of the aortic valve. The electrocardiogram was typical of the pattern associated with left ventricular strain.

The diagnosis was rheumatic heart disease, enlarged heart, mitral stenosis, mitral insufficiency, aortic stenosis, aortic insufficiency and tricuspid stenosis; regular sinus rhythm and class IV (classification of New York Heart Association).

There was considerable improvement in response to cardiac therapy but after ten days he insisted on leaving the hospital. One month later he was readmitted and stated he had been confined to bed at home most of that month and had taken his medication, 0.2 Gm. digitalis, daily. However, the dyspnea, orthopnea and weakness increased. There were occasional chest pains as before. His physician finally advised him to return to the hospital. This time he appeared very tired, dyspneic and slightly orthopneic. There was some cyanosis of the face and nail beds. Jaundice was not present. The physical findings were about the same as recorded one month before on the previous admission. There were more rales at both lung bases.

The neck veins were distended and pulsations were visible. The strong presystolic pulsation felt in the jugular area was again noted to "see-saw" with the systolic impulse felt in the suprasternal notch. The enlarged liver and its pulsations were felt. The diastolic murmur was again heard to the right of the lower sternum. Icterus index was 10. The electrocardiogram revealed no significant changes from the one previously described. Because of a rise in temperature to 101F.° on the second day a blood culture was taken but found sterile. The patient this time failed to respond to therapy; symptoms increased and rales at the lung bases became more numerous. The temperature rose to 103°F. on the fourth day and the patient succumbed on the next, the fifth day of the second admission, apparently of cardiac failure and possible hypostatic pneumonia or pulmonary infarction.

Postmortem examination was performed by Dr. Henry Brody. The veins in the neck were unusually distended, sufficiently so on the left to make prominent one of the valves in the external jugular vein. The pericardial sac was markedly distended, containing 300 cc. of clear, light yellow fluid. The pericardial surfaces were smooth and glistening. The heart weighed 800 Gm.; it was roughly quadrilateral, measuring 16 by 16 cm. The anterior surface was made up almost equally by the right and left ventricles. The tips of the auricular appendages, both right and left, also appeared in the anterior view. The right atrium showed marked roughening and thickening of its epicardial surface. The diameter was but slightly increased; the trabecular markings were very prominent. A very small organized thrombus was present in the tip of the auricular appendage. The tricuspid valve was partly stenosed, not admitting two fingers. It was roughly elliptical, the axes measuring 2 and 1 cm., respectively. There was complete fusion of the valves at the commissures so that the individual cusps could not be distinctly recognized. The valve was thickened, irregularly nodular and somewhat stiffened. The chordae tendinae were only slightly thickened. They did not appear shortened. The right ventricle was small. The columnae carneae appeared moderately rounded. The chamber was filled with a large amount of postmortem clot.

From the ventricular aspect the thickening and deformity of the line of closure of the tricuspid valve were quite prominent. The right ventricular myocardium measured 5 mm. in thickness in the region of the outflow tract. The circumference of the pulmonic valve was 6 cm. The posterior cusp in its left half was folded so that the normal free edge was adherent to the pulmonic surface of the valve. The new edge so formed was thick and showed a number of pinhead, glistening, grayish-white nodules. There was some thickening of the adjacent left cusp. The pulmonary artery showed only small, early atheromatous plaques. The left atrium was slightly dilated, its wall rather markedly thick-

ened. The foramen ovale was closed. The left auricular appendage was negative. There was some ridging and wrinkling of the atrial endocardium posteriorly. The mitral valve was narrowed, forming a somewhat curved slit slightly less than 3 cm. in length. Its ring was completely calcified, forming knobby protrusions into the lumen. On the endocardium were seen a number of smaller than pinhead, glistening nodules.

The left ventricle showed some degree of dilatation. The columnae carneae were definitely flattened. There was very marked hypertrophy of the wall, reaching a thickness of 18 mm. From the ventricular surface the marked stenosis and insufficiency of the valve was very striking. The chordae tendineae were markedly thickened but appeared stretched rather than flattened. A small moderator band was present, extending from the anterior surface to the mid-portion of the interventricular septum. There was marked graying and thickening of the endocardium of the interventricular septum immediately below the aortic valve. The aortic valve could best be viewed from above. The size of the lumen was entirely fixed due to calcification of the valve cusps. The lumen was almost circular with an approximate diameter of 11 mm. The cusps and their commissures were markedly thickened, calcified and showed many calcific protruberances. The calcification along two of the commissures extended up the aorta for a distance of less than 1.5 cm. The wider of the two was 1.4 cm. Above these the ascending portion of the aorta was relatively free of any change except for a band of yellow atheroma-like deposit, 1 cm. wide and 5 cm. in length. There was also an area about 1 cm. in diameter which showed small, glistening, reddish elevations. The coronary orifices were not involved in the calcific process. The coronary arteries in their first portions were markedly sclerotic and in places calcified. There was, however, no serious impairment of the lumen at any point, and no ulcerations or thrombi.

In the lungs there were a few, small, fresh hemorrhagic infarcts at both bases; the pulmonary arteries showed practically no atherosclerotic change. There were 100 cc. of light orange, clear fluid in the right pleural cavity and less than 200 cc. in the left.

The liver weighed 1,180 Gm.; it measured 22 by 18 by 7 cm. Its markings were somewhat accentuated; lobulations were distinct.

Microscopically, sections of the heart showed no evidence of active rheumatic inflammation. Perivascular, mostly acellular scars were numerous. The endocardium showed fibrous thickening; the muscle fibers showed hypertrophy. Sections of lung, liver, spleen and kidney showed chronic passive congestion.

## COMMENT

Venous phenomena are usually mentioned in descriptions of tricuspid valvular disease. The veins of the body are engorged and dilated and the pressure therein increased. The veins in the neck are of particular concern. The prominent "a" wave in the jugular sphygmogram has been frequently referred to, as has the presystolic impulse in the veins of the neck and in the liver. The marked and chronic systolic pulsations of the deep jugular veins, a "vigorous pulsation raising the sternocleidomastoid," has been emphasized by White and Cook[3,6] although they also indicated the absence of notable pulsation in the neck veins and liver in some cases.

Mackenzie[9] told of one case in which a large wave was sent back from the hypertrophied auricle with such force that it caused the valves in the jugular and subclavian veins to close with a snap which he heard over these veins as a clear, sharp sound preceding the first heart sound.

Some believed that without knowing the time of the pulse waves in the neck (or liver), the clinical diagnosis of tricuspid stenosis was not warranted. Wolferth[8] emphasized that the characteristic impulse in the veins in the neck in tricuspid stenosis should be presystolic. Crighton Bramwell has indicated the diagnostic value in tricuspid stenosis of a powerful auricular impulse which he recorded in the jugular sphygmogram.[10] With auricular fibrillation the presystolic impulse is lost, and in nodal rhythm its timing is different.

In our case, demonstrated at necropsy to have tricuspid stenosis, a marked presystolic impulse was felt over the right jugular vein just above the clavicle and over the sternocleidomastoid muscle. This

FIG. 1. Position of hands to elicit impulses over the jugular vein and episternal notch.

was of surprising force for a venous pulse. It was easily timed by comparison with the systolic aortic impulse in the episternal notch palpated by the index finger of the other hand. (Fig. 1.) A see-saw movement was conveyed to the two palpating fingers by the two vascular pulsations. The strong presystolic venous impulse over the jugular vein was considered caused by the contraction of the hypertrophied right atrium; this impulse was well transmitted to the neck because of the obstruction at the stenotic tricuspid orifice causing a damming-back action, the right atrium being unable to empty itself readily. Transmission of the impulse was also aided by the increased venous distention and increased pressure in the large veins central to this area. We have never felt a presystolic impulse in the jugular vein in congestive heart failure without tricuspid stenosis. The systolic impulse in the episternal notch due to the pulsation of the adjacent dilated aorta and innominate artery was undoubtedly modified by the aortic valvular disease present. It is increased by the insufficiency of the valve though decreased by the stenosis, lesions which accompany most cases of tricuspid stenosis.

SUMMARY

A simple sign characteristic of tricuspid stenosis is described. A case of tricuspid stenosis with necropsy findings is reported in which this sign led to the correct antemortem diagnosis.

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# Diaphragmatic Hiatus Hernia*

## *With Severe Iron-deficient Anemia*

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THAT diaphragmatic hiatus hernia is not a rare anatomic variation, as earlier medical literature seemed to indicate, is now well established. Improved methods of diagnosis and increased awareness of the condition have brought it to the foreground during the past several years. Giffin[15] in 1912 was able to collect a total of only 650 proved cases from the literature of which but fifteen were diagnosed during life, and Pancoast and Boles[28] were able to find only thirty-two additional cases so diagnosed prior to 1923. These figures contrast strikingly with more recent reports. Harrington[18] found that at the Mayo Clinic alone 600 cases of diaphragmatic hernia were diagnosed between 1926 and 1941. According to Murphy and Hay[25] the incidence of hiatus hernia in gastrointestinal x-ray studies done by various authors has varied from 0.75 to 2.9 per cent. Mendelsohn[23] found sixteen cases in 1,000 consecutive gastrointestinal studies for an incidence of 1.6 per cent, while Schatzki[30] reported an incidence of 3.5 per cent in 1,500 gastrointestinal roentgen examinations.

The esophageal hiatus type is the most common form of diaphragmatic hernia. Of the 295 cases that Harrington[18] treated surgically, 223 were at the esophageal hiatus. The remainder occurred in the following order: left hemidiaphragm forty-one, short esophagus type fourteen, hiatus pleura peritonealis seven, absent posterior fourth of the left diaphragm five, foramen Morgagni four, right hemidiaphragm one. The stomach was the only organ involved in 231 of these cases, and participated with various other organs of the peritoneal cavity in an additional fifty-five cases, being involved in 286 out of 295 cases.

Diaphragmatic hernia typically occurs in the short, stocky, middle-aged, multiparous female. The symptoms are so variable that the condition may masquerade as almost any disease of the upper abdomen or chest. Most common diagnostic errors in order of frequency, according to Harrington,[18] were cholecystitis, cholelithiasis, gastric ulcers, duodenal ulcers, hyperacidity, secondary anemia, cardiac disease, cancer of the cardia, stricture of the esophagus, appendicitis and intestinal obstruction. There are certain clinical manifestations, however, which should enable the clinician to diagnose or, at least suspect, the presence of a hiatus hernia in some instances. The more common abdominal symptoms[1,16,19,26] in order of frequency are epigastric pain, a feeling of distress during or after meals and associated with bloating, belching, heart burn, nausea, vomiting and regurgitation, night pain or pain in the recumbent position, dysphagia and hiccough. Hiatus hernia has often been confused with anginal symptoms and coronary artery disease[11,12,20,21] because of the presence of substernal pain with occasional radiation of the pain to the left arm.

Definitive diagnosis of diaphragmatic hernia is, of course, made on the basis of x-ray findings. The diagnosis of the larger

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hernias, with all or a good portion of the stomach in the thoracic cavity, is very easy roentgenologically. The smaller or reducible hernias are likely to escape discovery unless the examiner is alert for clues that will stimulate careful study. Such clues, according to Harrington,[17] are (1) displacement of the lower segment of the esophagus, (2) a tortuous but not dilated terminal esophageal segment, (3) angulated segment, (4) undue retardation of the barium stream at the hiatus, (5) level of gastric contents above the esophageal aperture, (6) what apparently is high hour-glass contraction of the stomach with a visible niche at the site of constriction is, in fact, often a hernia of the stomach through the diaphragm with the ulcer merely a complication.

In spite of the increasing frequency with which hiatus hernia is recognized, sufficient emphasis has not been placed on its ability to produce a profound anemia.

There are many reports describing gastric ulcers in the herniated portion of the stomach. Bright[5] is credited with the first description in 1836. Carman and Fineman[6] in 1924 were probably the first roentgenologists to mention bleeding and anemia which occurred in three of their twenty cases diagnosed by x-ray. Öhnell[27] in 1926 was the first to point out the correlation between hiatus hernia and bleeding. Bock,[3] in a discussion of one of the Cabot cases in 1929, emphasized the relationship between gastrointestinal hemorrhage and hiatus hernia. He cited three cases in which occult blood was found in the stools and an anemia was present. The only abnormal roentgenologic findings were those of hiatus hernias. In 1933 Gardner[14] reviewed the English literature on anemia associated with hiatus hernia. He was able to collect twenty-two previously published cases including those reported by Segal,[33] Mathews and MacFee[22] Weitzen[37] and Truesdale.[35] To these he added six unpublished cases making a total of twenty-eight. Of these seventeen were females and eleven males. Nineteen patients were over forty years old and fourteen had demonstrable loss of blood. Bock, Dulin and Brooke[4] in 1933 reported a series of ten patients. They emphasized the "silent" nature of this condition, the absence of physical signs and the tendency to recurrent bleeding. In their series there were nine females and one male, their ages ranging from fifty-one to seventy-nine years. Moersch[24] noted the presence of gastrointestinal bleeding with weakness and evidence of anemia in thirty-two of the 246 patients with hiatus hernia encountered at the Mayo Clinic from 1932 to 1937. In this series there were 133 females and 113 males. The average age was fifty-five, the youngest eight and the oldest eighty-two. Cowan's[9] observations were based on forty-five cases studied from 1930 to 1935 at Mount Sinai Hospital, New York. He had thirteen cases in the "severe secondary anemia" group. His comments regarding these are pertinent: "In the anemia group the presenting symptoms are those usually associated with severe anemias such as weakness, anorexia, dyspnea and pallor. Very few if any gastric symptoms are in association with the anemia. The case histories of all these patients show the presence of a long-standing secondary anemia with evidence of bleeding from the gastrointestinal tract *not due* to ulcers, varices, or any other organic disease."

Murphy and Hay[25] in 1943 reported on seventy-two patients with hiatus hernia at the Peter Bent Brigham Hospital. There were sixty-one women and eleven men. The average age was sixty, the youngest thirty-three and the oldest seventy-eight. Hemoglobin values were available for sixty-seven of the patients and of these twenty-three had levels below 10 Gm.

Among other clinicians who have commented on the relationship of anemia to hiatus hernia are Schiro and Benjamin,[31] Sahler and Hampton,[29] Ohler and Ritvo,[26] Weinberg,[36] Mendelsohn,[23] Dyke and Dyas,[10] Trueman[34] and Andrews.[1]

Bleeding has even been observed in infants. Christiansen[8] in 1937 reported a case of hiatus hernia associated with hematemesis in a one year old child. Bergenfeldt[2] reported a case of hematemesis in an eight-

een month old boy in whom there was cessation of bleeding after repair of the hiatus hernia.

The anemia accompanying hiatus hernia is due to any or all of the following causes: (1) passive congestion, (2) ulcer due either to varicosities resulting from passive congestion or a disturbed blood supply and (3) inflammation in the region of the wall of the viscera incarcerated in the hiatus of the hernia. Boch et al.[4] demonstrated by operative and postmortem examination that in the great majority of their cases the cause of bleeding was due to simple congestion of the mucous membrane and some enlargement of the veins in the walls of the herniated portion of the stomach. The mucosa in the non-herniated portion appeared normal. Gastric ulcers occurring in the herniated portion of the stomach have been reported by Mathews and MacFee,[22] Truesdale,[35] Feldman[13] and Harrington.[17] Harrington states that "the ulcer is due to trauma and is usually situated in the lower end of the esophagus close to its juncture with the stomach and it may be found in that portion of the stomach in the hernial sac near the lesser curvature. These traumatic ulcers result from the to and fro action of the stomach in the hernial ring when the hernia is small as well as from the forceful pressure exerted on the large distorted and congested stomach during the attacks of vomiting when the hernia is large. There is also the additional factor of regurgitation of gastric juices into the lower part of the esophagus which produces esophagitis . . . After repair of the hernia and replacement of the stomach into its normal position most of these traumatic ulcerations heal spontaneously." Commenting on the type of bleeding from these traumatic erosions he states that they may be severe, and hematemesis or melena is often one of the chief signs. In other instances the patient may not be aware of any blood loss and yet have a very marked anemia resulting from occult bleeding. This type occurred in 11 per cent of his series.

Chevallier and Danel[7] suggest that the anemia is caused by a torpid inflammatory process in the affected region of the gastric wall.

### CASE REPORTS

Case I. S. F., a sixty-one year old white female, complained of pain in the legs, especially at night; palpitation and "nervousness" for several years; occasional episodes of "heartburn"; precordial pain with radiation down the left arm, not related to exertion but relieved by sodium bicarbonate. Her menopause occurred at the age of fifty-four with no subsequent bleeding. Diagnosis of esophageal hiatus hernia was made at the age of fifty-seven. At that time her blood count was as follows: hemoglobin 50 per cent, red blood cells 4.00, white blood cells 9,600, differential within normal limits. X-ray showed an unusually large cardio-esophageal hiatus hernia, the size of a lemon, projecting above the diaphragm into the retrocardiac space, with the esophagus invaginating into the hernia. The rest of the gastrointestinal tract was normal on x-ray examination. Arthritic changes were noted in the lower cervical intervetebral spaces and also in the lumbar spine. Stool examinations were consistently negative for occult blood.

She was first seen by the senior author at the age of fifty-nine. The symptoms had not significantly changed. Physical examination revealed a very pale, obese white female. Except for a soft systolic murmur over the pulmonic area the remainder of the examination was essentially negative. Her hemoglobin now was 33 per cent (5.1 Gm.), red blood cells 4.08, white blood cells 12,700, hypochromia 3+, anisocytosis 4+, polychromatophilia 1+, poikilocytosis 4+. The differential count was: polymorphonuclears 64 per cent, lymphocytes 24 per cent, monocytes 10 per cent, basophils 1 per cent, eosinophils 1 per cent. The presence of the hiatus hernia was confirmed. (Fig. 1.) She was given ferrous sulfate and improved satisfactorily hematologically. About a year later, following intermittent iron therapy, she had 83 per cent (12.9 Gm.) hemoglobin and 4.44 red blood cells. Stools were intermittently positive for occult blood. When last seen she had a hemoglobin of 92 per cent (14.4 Gm.) and red blood cells 5.11.

Case II. H. S., a fifty-three year old white female, complained chiefly of dyspnea on the slightest exertion for two months; hair quite dry, nails "break in layers" for months; and

FIG. 1. Large cardio-esophageal hiatus hernia, Case I.

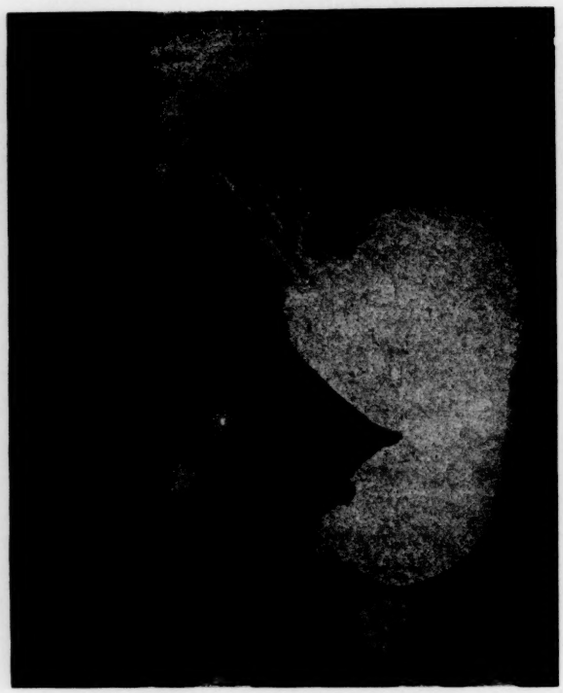


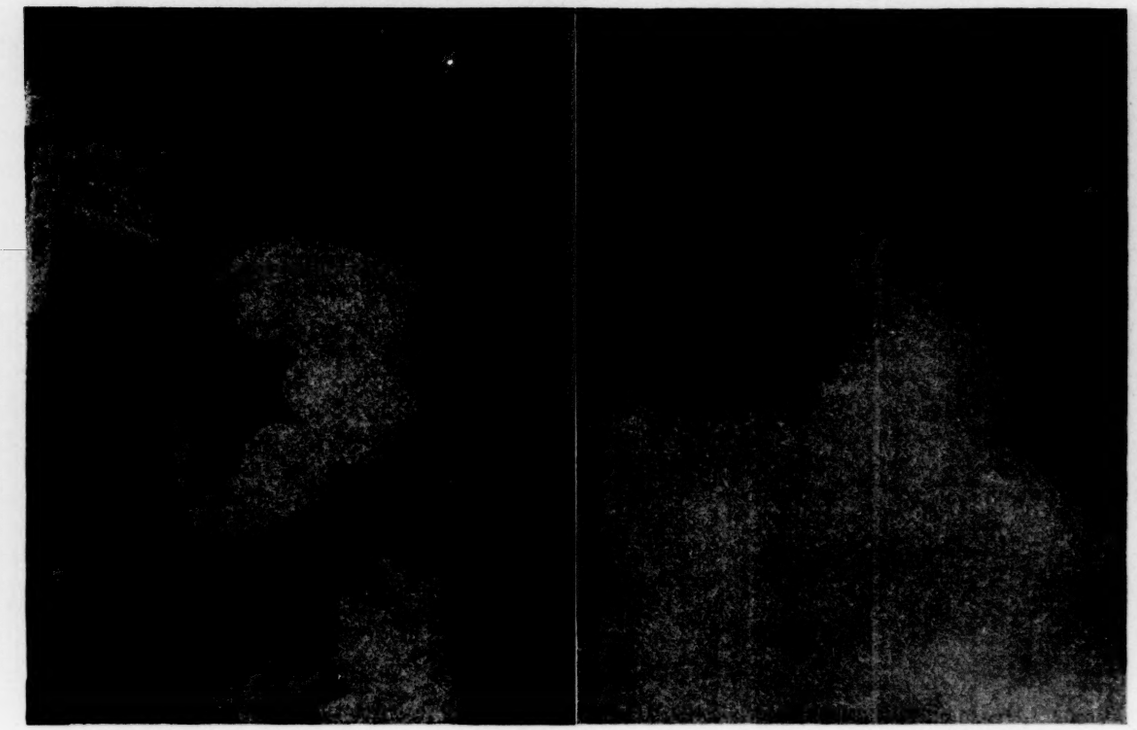
FIG. 2 Large hiatus hernia, Case III.

numbness in the fingers especially during the mornings. Her past history revealed that she had an induced menopause eight years previously, hypertension for the last few years and an 80 per cent hemoglobin a year before. Her diet had been adequate and there had been no known source of bleeding. Positive physical findings were the pallor, an uncoated tongue with a moderate atrophy of the papillae and the fragile but not very thin nails. Blood findings were: hemoglobin 41 per cent (6.5 Gm.), red blood cells 3.21, white blood cells 6,250, microcytosis, anisocytosis, poikilocytosis and hypochromia were moderate, platelets were increased; polymorphonuclears 60 per cent, lymphocytes 26 per cent, monocytes 7 per cent, eosinophils 6 per cent, basophils 1 per cent. Roentgenologic examination of the gastrointestinal tract was negative except for a "large hiatus hernia of the stomach. The portion of the stomach in the hernia showed coarse mucosal folds and there was a spot in the front showing conversion of the mucosal folds which is suspected to be an ulcer crater." The patient has done well clinically on ferrotherapy.

CASE III. T. J., an eighty-three year old, white female, complained chiefly of easy fatiguability. She was under treatment for hypertensive heart disease for several years. Physical examination revealed a rather pale, obese, white female. Except for the enlarged left heart and the elevated blood pressure nothing remarkable was found. Blood findings were: hemoglobin 40 per cent (6.3 Gm.), red blood cells 2.50, white blood cells 7,500, platelets adequate, polymorphonuclears 58 per cent, lymphocytes 38 per cent, monocytes 4 per cent, anisocytosis 2+, poikilocytosis 2+ and hypochromia 2+.

Roentgenologic examination of the gastrointestinal tract disclosed a large hiatus hernia of the stomach with a small diverticulum at the greater curvature side of the herniated portion of the stomach. (Fig. 2.) No intrinsic lesion was noted in the stomach or the duodenum. The patient was given iron therapy and showed a gratifying clinical and hematologic response.

CASE IV. A seventy-seven year old white female, complained of palpitation, shortness of breath and tiredness. For six months she had been in bed most of the time. She was found to have severe anemia four years previously when, at the time of her pneumonia, she had three blood transfusions. Eighteen months before she was hospitalized for a rectal abscess and again had two transfusions because of anemia. A blood count at that time showed the following: hemoglobin 19 per cent (2.9 Gm.), red blood cells 2.49, white blood cells 11,450, polymorphonuclears 77 per cent, lymphocytes 16 per cent,



3 4

FIG. 3. Large hiatus hernia, Case IV.
FIG. 4. Elevation of right diaphragm which was interpreted as "an unusual domed separate diaphragmatic leaf." This patient had the large diaphragmatic hernia shown in Figure 3.

monocytes 7 per cent, hypochromia 4+, anisocytosis 4+, poikilocytosis 2+. She was given weekly "shots" after being discharged from the hospital and took eight Lextron capsules a day for a few months. Physical examination revealed an obese, pale, white female. A blowing systolic murmur was present at the mitral and aortic areas. The nails were soft and the hair was dry and moderately coarse. The remainder of the physical examination was negative. Blood count at this time revealed hemoglobin 56 per cent, (8.7 Gm.), red blood cells 3.39, white blood cells 11,800, platelets increased, polymorphonuclears 78 per cent, lymphocytes 15 per cent, eosinophils 2 per cent, monocytes 5 per cent, hypochromia 2+, microcytosis 2+.

Chest x-rays at the time of the pneumonia revealed in addition to the pulmonary consolidation "a radiolucent shadow with a horizontal fluid level lying just behind the apex of the heart and which probably represents a diaphragmatic hernia with a fluid level." (Figs. 3 and 4.) This was subsequently confirmed by barium meal. The patient was again given iron therapy and has done well since.

CASE V. L. C., a seventy-seven year old white female, experienced a sudden onset of weakness, malaise, anorexia and continuous borborygmi ten days prior to her admission. The following day she noted tarry stools. After that she remained weak and tired, had marked nausea, pain in the right upper quadrant and swelling of the upper abdomen. Twenty years before she had "yellow jaundice" which disappeared spontaneously and for eighteen years she received therapy for a very "bad liver." Selective dyspepsia to sauerkraut, fried foods, etc., was noted by the patient. She was found to be very pale and obese. Her blood pressure was 180/70. An occasional inspiratory wheeze was heard in the bases posteriorly. The heart was moderately enlarged to the left; a soft systolic murmur was heard at the apex and a blowing systolic murmur at the aortic area. There was some tenderness in both the right and left upper quadrants. Examination of the blood revealed hemoglobin 27 per cent (4.4 Gm.), red blood cells 2.06, white blood cells 7,300. The stools were positive for occult blood. X-ray examination disclosed a diaphragmatic hernia with the cardiac portion

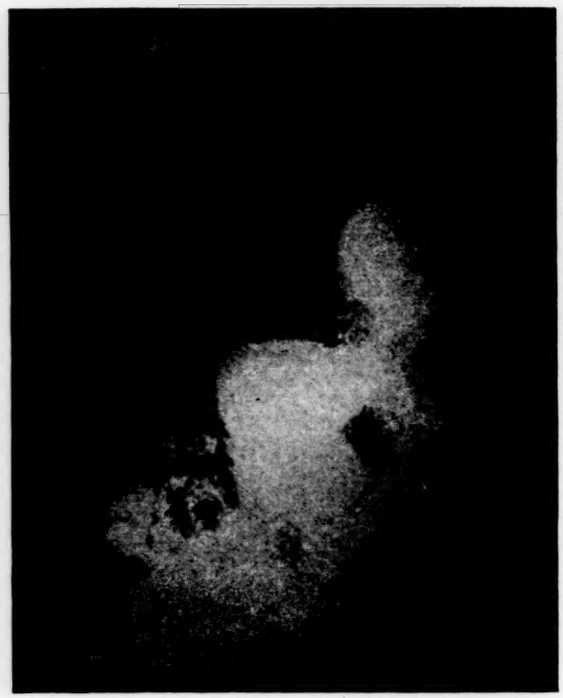


FIG. 5. Large diaphragmatic hernia, Case v.

of the stomach through the hiatus. No ulcerations or varicosities could be detected in the herniated portion of the stomach. (Fig. 5.)

She received four transfusions of blood and iron therapy. Improvement, however, was slow due to continuation of gastrointestinal bleeding.

CASE VI. C. N. B., a seventy-six year old white female, complained of increasing weakness, dyspnea on exertion of six months' duration and arthritis involving the lower dorsal vertebrae for ten years. There was no weight loss and no known blood loss. She was obese and very pale. Her blood pressure was 160/75. The remainder of the examination was not significant. Blood findings were: hemoglobin 31 per cent (4.8 Gm.), red blood cells 2.59, white blood cells 5,700, hypochromia 4+, anisocytosis 4+, poikilocytosis 1+, polychromatophilia 2+. Stools contained from a trace to 4+ occult blood. Roentgenologic examination revealed an esophagus foreshortened into a large hiatal hernia, the size of an orange.

There was a dramatic clinical and hematologic response to iron therapy.

CASE VII. M. D., a white female, approximately fifty years of age, complained of fainting spells, described as "blackout sensations," which lasted about five to ten minutes and occurred daily during the week before admission to the hospital. She also experienced dyspnea, palpitation on exertion and weakness during this period. No previous history was significant. Physical examination showed a moderately enlarged left heart with a systolic murmur in the mitral region. Blood findings were: hemoglobin 36 per cent (5.6 Gm.), red blood cells 3.43, white blood cells 10,300 with an essentially normal differential count. The red cell showed marked microcytosis and hypochromia. X-rays revealed that the barium passed to the lower third of the esophagus without hesitation. At this point the esophagus was tortuous and a diaphragmatic hernia was present. From this the barium passed freely into the stomach and filled it and the duodenal bulb without demonstrating further lesions. The patient discharged herself two weeks after admission but returned five days later because of a recurrence of the fainting spells. At this time her hemoglobin was 24 per cent and red blood count 2.24. She remained in the hospital for another week and again was discharged "against advice." Her further course is unknown.

CASE VIII. D. M., a sixty-four year old white female, complained of swelling of the legs, weakness, palpitation, pounding in the head, tiredness, numbness of the fingers and gastrointestinal upsets of two to three weeks' duration. The physical examination was non-contributory. Blood examination revealed: red blood cells 3.3, hemoglobin 30 per cent (4.7 Gm.), white blood cells 6,000, differential within normal limits, except for the red cells which showed marked microcytosis and hypochromia. X-ray revealed a hiatus hernia the size of an apple. The esophagus was normal in length and entered the diaphragmatic hernia posteriorly. Stools were positive for occult blood. The patient was given iron therapy and a bland diet on which she improved. Blood findings eight months later were: hemoglobin 12.5 Gm. and red blood cells 4.3.

CASE IX. B. A., a forty-one year old white male, complained chiefly of "fainting spells." The first episode occurred two years before admission, there being two the first year, three the second year and two the preceding month. The fainting spells were usually accompanied by profuse sweating and dizziness. He had lost 10 pounds in the last three months. There was no known history of bleeding. Physical examination revealed nothing of significance. He was obese and very pale; blood pressure was 130/80.

The blood findings were: red blood cells 3.23, hemoglobin 34 per cent (5.3 Gm.), white blood cells 8,500, polymorphonuclears 75, lymphocytes 15, monocytes 10. The red cells on smears were very small and hypochromic. Stools contained 2+ blood on repeated examinations. Roentgenologic examination disclosed that in the upright position the distal end of the esophagus was displaced to the right in the lateral view by what was interpreted as being stomach lying inferior to the diaphragm. In the Trendelenburg position a considerable portion of the stomach was seen to pass above the diaphragm into the chest and to lie superimposed on the spine and slightly to the right of it.

TABLE I
SUMMARY OF CASES I TO X

| No. | Name | Age | Sex | Lowest Known | | | Symptoms | | | X-ray Findings |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | RBC | Hgb. % | Color Index | Gastro-intestinal | Cardio-vascular | Other | |
| I | S. F. | 61 | F | 4.1 | 5.1 Gm. 33 | .40 | + | + | + | Large cardio-esophageal hiatus hernia |
| II | H. S. | 53 | F | 3.2 | 6.4 Gm. 41 | .68 | 0 | + | + | Large hiatus hernia with suspicious ulcer crater |
| III | T. J. | 83 | F | 2.5 | 6.3 Gm. 40 | .80 | 0 | + | + | Large hiatus hernia with a small diverticulum |
| IV | G. S. | 77 | F | 2.5 | 2.9 Gm. 19 | .38 | 0 | + | + | Large diaphragmatic hernia |
| V | L. C. | 77 | F | 2.1 | 4.4 Gm. 27 | .64 | + | 0 | + | Diaphragmatic hernia with herniation of cardiac portion of stomach; acute gastrointestinal hemorrhage the presenting symptom |
| VI | C. V. B. | 76 | F | 2.6 | 4.8 Gm. 31 | .60 | 0 | + | + | Foreshortened esophagus with large hiatus hernia |
| VII | M. D. | 50+ | F | 2.2 | 3.7 Gm. 24 | .55 | 0 | + | + | Diaphragmatic hernia |
| VIII | D. M. | 64 | F | 3.3 | 4.7 Gm. 30 | .45 | + | + | + | Diaphragmatic hernia with normal esophagus entering the hernia posteriorly |
| IX | B. A. | 41 | M | 3.2 | 5.3 Gm. 34 | .53 | 0 | 0 | + | Diaphragmatic hernia with normal esophagus; inconstant herniation of stomach into chest cavity |
| X | J. W. | 52 | M | 2.0 | 4.4 Gm. 28 | .70 | + | 0 | + | Large para-esophageal diaphragmatic hernia |

CASE X. J. W., a fifty-two year old white male, complained of weakness so marked that he could not stand long enough to finish shaving. He slept eighteen to twenty-two hours a day. The onset was gradual over a period of years but fairly more marked over the past two months. There was a vague history of hematemesis fifteen years previously following a strenous lecture tour. Some epigastric "burning" relieved by alkali on several occasions during the past year was admitted. Physical examination revealed nothing extraordinary excepting the marked pallor. Blood examination revealed red blood cells 2.0, hemoglobin 28 per cent, white blood cells 6,000, differential within normal limits, and increase in platelets; hematocrit was 16 per cent. The stools were positive for occult blood. X-ray of the stomach revealed a large para-esophageal diaphragmatic hernia in which no ulcer was demonstrable. Following 1,500 cc. of whole blood, a bland diet and ferrotherapy the patient was remarkably improved and has continued well to the present time.

## COMMENT

The analysis of our cases merely re-emphasizes the presence of certain charac-

teristic features associated with gastric hiatus hernia. It is known to be a condition most commonly found past middle age, predominantly in short, stocky, obese females. Our patients averaged about sixty-three years and with three exceptions were over 50. Twelve of the twenty were females.

Physical examination revealed nothing extraordinary except marked pallor and obesity. This absence of physical findings, evidence of weight loss, masses, tenderness or resistance in the abdomen became important clues in the recognition of the cases clinically in the last group of cases.

TABLE II

SUMMARY OF CASES XI TO XX

| No. | Name | Age | Sex | Lowest Known | | | Symptoms | | | X-Ray Findings | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | RBC | Hgb. % | Color Index | Gastro-intestinal | Cardio-vascular | Other | | |
| XI | W. S. | 40 | M | 2.15 | 4.7 Gm. 30 | .69 | + | + | 0 | Diaphragmatic hernia | Tarry stools |
| XII | B. R. | 48 | F | 2.82 | 4.8 Gm. 31 | .55 | + | 0 | + | Large hiatus hernia | |
| XIII | L. M. | 53 | F | 3.30 | 5.3 Gm. 34 | .51 | + | + | + | Diaphragmatic hernia of cardia | Autopsy proved |
| XIV | J. D. | 65 | M | 3.36 | 6.7 Gm. 43 | .64 | + | 0 | 0 | Small diaphragmatic hernia | Hematemeses; hernia surgically repaired and a shortened esophagus was found |
| XV | E. B. | 66 | M | 1.68 | 2.2 Gm. 14 | .42 | 0 | 0 | + | Diaphragmatic hernia | |
| XVI | S. S. | 69 | M | 2.50 | 6.5 Gm. 42 | .84 | + | 0 | + | Diaphragmatic hernia | Tarry stools |
| XVII | A. H. | 71 | F | 2.45 | 3.9 Gm. 25 | .51 | + | + | + | Diaphragmatic hernia with large ulcer crater in herniated portion of stomach | |
| XVIII | J. D. | 72 | M | 2.79 | 3.9 Gm. 25 | .44 | + | + | + | Large hiatus hernia involving cardia of stomach | "Bloody stools" |
| XIX | F. G. | 72 | F | 2.40 | 6.7 Gm. 43 | .89 | 0 | + | + | Small hiatus hernia | "Bright red blood in stool"; x-ray examination of gastro-intestinal tract (except hernia) negative; proctoscopy negative |
| XX | D. M. | 81 | M | 2.97 | 7.3 Gm. 47 | .78 | + | 0 | + | Diaphragmatic hernia | Tarry stools |

Their general appearance fitted well the accepted prototype. (Tables I and II.)

Interesting in the histories was the paucity of gastrointestinal symptoms. Twelve patients had complaints referable to the abdomen but these were seldom marked. Cardiovascular symptoms were much more prominent, being present in all but eight patients. Their nature was variable and had its genesis partly in the anemia and partly in the degenerative changes present incidental to the advanced age. The other symptoms were divisible into those related to the hiatus hernia and consequent anemia and those simply co-existing. Among the former might be mentioned weakness, dryness of the hair, splitting of the nails and coldness and numbness, while among the latter were "nervousness," arthritic pains and selective dyspepsia.

Our attention was focused on the remarkable anemia present in every instance, which indirectly was responsible for the patient consulting a physician and which in turn gave an early clue to the nature of the disability. In this connection the red blood cell count is of relatively little value, as we have pointed out previously,[32] except that it aids in the determination of the color index. The physiologic severity of the anemia is indicated by the hemoglobin level which varied from 2.2 to 7.3 Gm. (14 to 47 per cent). The fact that all these patients were ambulatory, indicating a gradual adjustment to the low hemoglobin, and that the color index in most cases was very low, signifies that the bleeding was of a duration long enough not only to have depleted the body's iron stores but also to have dissipated a goodly portion of the circulat-

ing hemoglobin. In all instances in which the color index was greater than 0.7 (except Case III) recent acute blood loss, as manifested by tarry stools or hematemeses, complicated the chronic bleeding.

In only two cases was an ulcer crater seen. The bleeding is apparently quite irregular and unpredictable. The same patients, under what appeared to be the same conditions, showed anywhere from none to 4+ occult blood. Since all patients were thoroughly studied for other gastrointestinal bleeding lesions and none were found, and since most have been followed for a time sufficient to have revealed an early or small bleeding neoplasm, it may be assumed that the bleeding actually was from the herniated portion of the stomach. This is further borne out by the frequency with which blood was found in the gastric contents when examined. The response to iron therapy was gratifying as was expected since we were dealing with a relatively pure iron deficiency and since the rate of loss was far less than regenerative capacity.

## SUMMARY

Twenty patients with diaphragmatic hiatus hernia were studied. Bleeding from the stomach in these patients resulted in severe iron-deficient anemias. There was a paucity of symptoms directing attention to the gastrointestinal tract but cardiovascular symptoms were quite prominent. Physical findings were negligible.

In a patient, especially a female past middle age, who presents an iron-deficient type of anemia without a history of bleeding, localizing symptoms and physical findings of significance, a diaphragmatic hiatus hernia should be suspected and ruled out.

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# Biologic Complications of Penicillin Therapy*

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Not long after the introduction of sulfonamide compounds a variety of untoward reactions was encountered. Like other drugs with a relatively low therapeutic index these reactions took the form of drug fevers, rashes, hematologic and urologic complications and, in large measure, have been responsible for some caution in their general use. In a broad sense a more interesting complication of sulfonamide medication has been the development during the past decade of drug resistance by some strains of bacteria, notably the gonococcus. Since the sulfonamides have not been as powerful antibacterial agents as penicillin, this ecologic rumbling has only suggested the violent shifts in host-parasite relationships which may follow the use of drugs with extremely high therapeutic indices. Like the sulfonamides, penicillin also is a double-edged weapon against disease.

In the doses we use the common allergic drug reactions are not encountered unless the drug is taken locally or orally. In certain other situations, however, indirect reactions of a biologic nature, depending upon the alterations in bacterial flora, are now being seen. For example, vitamin deficiencies may be induced by changing the bowel flora,[1] resistant strains of bacteria may replace the organisms found in the respiratory and genito-urinary tract[2–5] and finally strains of bacteria normally absent or present in small numbers may cause acute illness[6–8] or even death. The purpose of this paper is to cite examples of this latter type of complication following penicillin therapy. Although these are single examples and represent an unusual therapeutic difficulty, they emphasize the importance of using penicillin with the same careful clinical indications with which we apply other, less spectacular remedies.

## CASE REPORTS

CASE I. M. D. (No. 81365), a sixty-eight year old white female, entered the hospital on August 27, 1946, because of persistent vomiting, periumbilical pain and weight loss of three weeks' duration. A posterior gastro-enterestomy had been performed in 1931 for a poorly controlled gastric ulcer. She had been well until postprandial epigastric pain recurred in 1945, at which time a gastrojejunal ulcer was demonstrated by x-ray. Three weeks before admission weight loss, anorexia, pain and vomiting recurred. The remainder of the past history was non-contributory.

Physical examination revealed a poorly nourished elderly woman complaining of abdominal discomfort. Temperature was 98°F. (54.4°C.), pulse 112, respirations 22 and blood pressure 120/75 mm. Hg. The chest was moderately emphysematous and hyper-resonant to percussion. Examination of the lungs and heart was otherwise unremarkable. The abdomen showed only direct periumbilical tenderness. The remainder of the examination was negative.

The blood Hinton test was negative. Examination of the urine and the stool guaiac test were negative. On admission hemoglobin was 11 Gm. per cent, hematocrit 34 per cent, white blood cell count 8,500 with a normal differential. Blood chemical values were not remarkable. A gastrointestinal series revealed a jejunal ulcer. Electrocardiogram showed premature auricular contractions.

On a Sippy II diet, high protein drinks and intravenous fluids the patient improved but symptoms persisted and the nightly gastric

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residue was 500 cc. On the sixteenth hospital day prophylactic penicillin, 40,000 units every four hours intramuscularly, was started and a subtotal gastric resection with a Polya type anastomosis was performed. The immediate postoperative course was satisfactory. On the second postoperative day the patient's temperature rose to 103°F. and the patient became cyanotic. The trachea and heart were shifted to the left and there was dullness at the left base. The white cell count was 1,150 per cu. mm. with 32 per cent polymorphonuclear leukocytes. An electrocardiogram showed sinus tachycardia. In spite of oxygen, morphine, heparin and penicillin the patient remained in semi-shock for twelve hours and then expired.

Postmortem examination performed three hours after death revealed a confluent bronchopneumonia of the lower two-thirds of the left lung with a small left hydrothorax. The lung had the consistency of soft liver. Five microscopic sections showed an acute cellular reaction and many bacilli, both free and within phagocytes. Multiple cultures of the involved pulmonary tissue yielded a pure growth of Bacterium coli. No other pathologic cause for death was found.

*Comment.* An elderly woman with pulmonary emphysema who was treated with prophylactic penicillin therapy in the course of a gastric resection for intractable ulcer symptoms developed an overwhelming bronchopneumonia and died two days postoperatively. Postmortem examination revealed as the cause of death an extensive bronchopneumonia due to Bact. coli.

CASE II. H. K. (No. 82287), a sixty-seven year old white male, was admitted to the hospital on December 14, 1946, with a diagnosis of carcinoma of the stomach. During the previous eight months the patient had had continuous epigastric pain associated with anorexia, constipation and a weight loss of 30 pounds. The diagnosis of gastric cancer had been made but because of an unexplained anemia and leukopenia operation had been delayed. Three days before admission the patient became completely obstructed. The past history was non-contributory.

On entry the temperature was 99.4°F. (44.2°C.), pulse 90, respirations 20 and blood pressure 112/55 mm. Hg. The patient was an emaciated, chronically ill, dehydrated elderly man. A few rales were heard at the left base of the lung. The heart was slightly enlarged to the left. The abdomen gave a sensation of fullness in the epigastrium but no mass was felt. The rectum contained impacted feces. The remainder of the examination was not significant.

The blood Hinton test was negative. Urine showed 1+ protein and 5 to 10 white blood cells per high power field. Hemoglobin was 10.2 Gm. per cent, white blood cell count 1,800 with 20 per cent neutrophiles and 80 per cent lymphocytes. Blood urea nitrogen was 26 mg. per cent and the serum total protein 5.7 Gm. per cent.

The patient was placed on intermittent Wangensteen suction, high protein drinks and was given parenteral fluid and vitamin therapy. With prophylactic sulfadiazine, 2.5 Gm. daily, and penicillin, 50,000 units intramuscularly every three hours beginning immediately before operation, a subtotal gastrectomy was performed on the fifth hospital day and the tumor was removed from its adherence to the pancreas. The early postoperative course was uneventful but the next day the patient had a shaking chill and the temperature rose to 104°F. There were numerous moist rales in both lungs and a chest x-ray was consistent with a widespread peribronchial pneumonia which was more widespread onthe right than on the left. The white blood cell count was 1,900 per cu. mm. The urine was clear. Sulfadiazine was discontinued and penicillin was increased to 50,000 units every two hours. At no time did the patient vomit. His condition deteriorated in spite of oxygen and blood transfusions. Shock supervened and the patient expired on the eighth hospital day.

At the autopsy performed four and one-half hours postmortem the cause of death was found to be marked bronchopneumonia involving all lobes of both lungs; it was interpreted as resulting from aspirated material. Four stained microscopic sections showed the alveoli to be filled with huge numbers of gram-positive and gram-negative bacteria, with a sparse cellular reaction. Three specimens of lung tissue grew Proteus vulgaris in pure culture and a fourth, Pseudomonas aeruginosa. There was no evidence of metastatic disease and the operative site was intact.

*Comment.* An emaciated elderly man with adenocarcinoma of the stomach had a gastric resection with prophylactic penicillin therapy. Postoperatively the patient de-

veloped fatal bronchopneumonia which failed to respond to larger doses of penicillin. Autopsy revealed extensive pneumonia due to P. vulgaris.

CASE III. C. P. (No. G5420) (Figs. 1 to 2B) a sixty-nine year old, white, retired toolkeeper was admitted to the hospital on October 19, 1947, because of fever, cough and dyspnea. During the previous ten years the patient had had a chronic productive cough without hemoptysis and had had four bouts of bronchopneumonia. He had drunk alcohol heavily for years. For three years he had been maintained on digitalis with fair cardiac compensation. For two years the patient had not been working. Six days before admission he noted an increase in his cough. On the day before admission he developed a fever of 102°F. and became delirious.

Physical examination on admission revealed an acutely ill, moderately well oriented man, dyspneic, slightly cyanotic and dehydrated. The temperature was 103°F. (57.2°C.) by rectum, pulse 126 and regular, respirations 36 and blood pressure 140/70 mm. Hg. The tongue was coated and the pharynx reddened. The trachea was in the midline. The chest was emphysematous; there was decreased expansion of the left lung with dullness, bronchovesicular breath sounds and sticky inspiratory rales over the right middle and both lower lobes of the lungs. The heart showed sinus tachycardia which was confirmed by electrocardiography. The abdomen was doughy and peristaltic sounds were markedly diminished. The liver and spleen were not felt. There was no clubbing or edema of the extremities.

The blood Hinton test was negative. The white blood cell count was 15,900 per cu. mm. with 96 per cent neutrophiles and the hematocrit was 50 per cent on admission. The urine contained 2+ protein and 6 to 10 white blood cells and occasional granular casts per high power field. Blood urea nitrogen was 68 mg. per cent. The sputum was green and tenacious, not copious in amount, and yielded in almost pure culture Pneumococcus type III, with rare alpha and beta hemolytic streptococci. Blood culture was negative. X-ray of the chest showed mottled areas of consolidation in the lower half of each lung field. (Fig. 2A.)

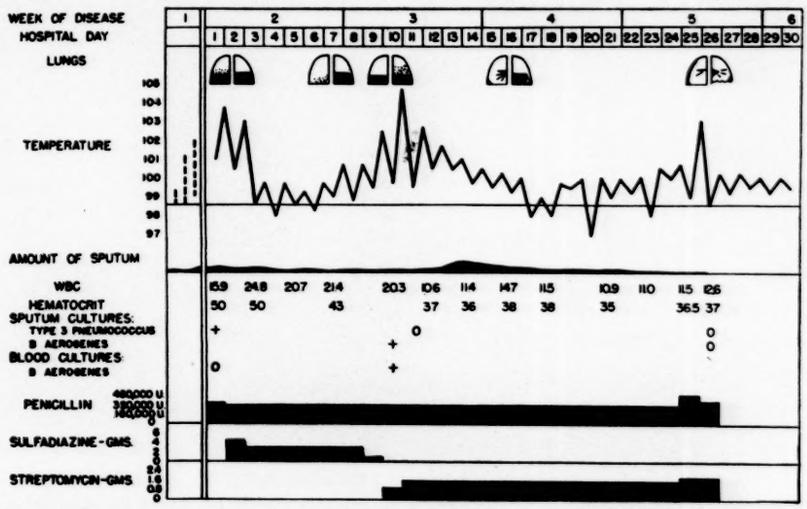
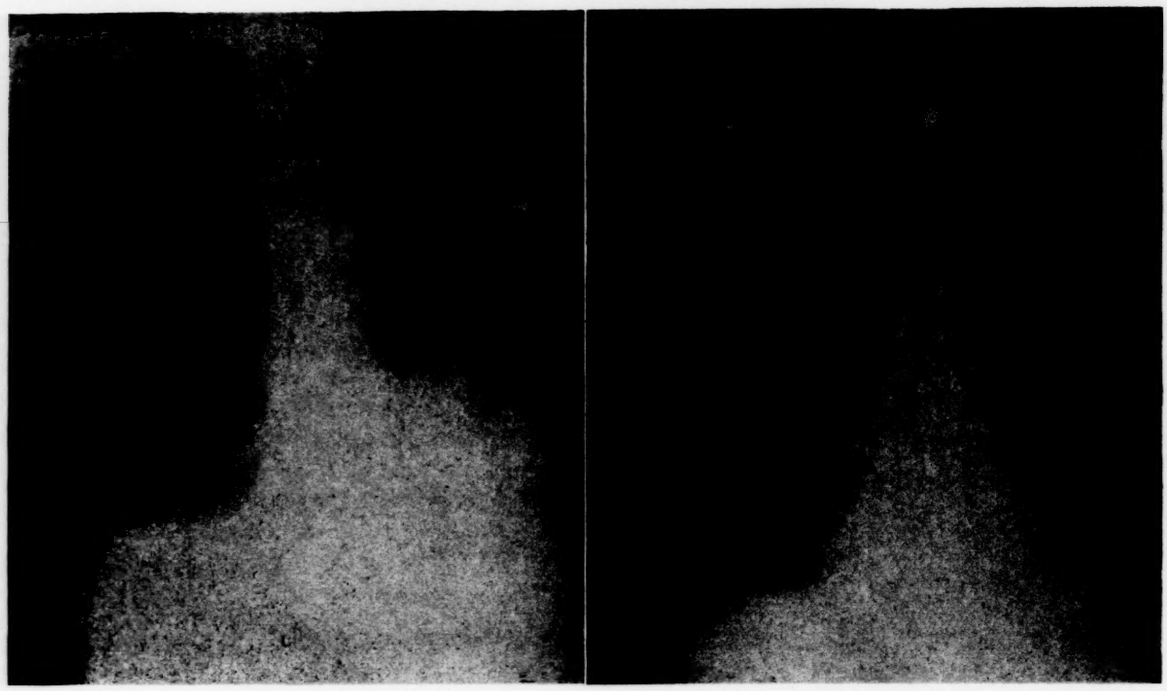



FIG. 1. Hospital course of Case III (C. P. Medical No. G5420). Note the gradual elevation in temperature to a high spike with chill on the tenth hospital day, concomitant with the recovery of pure cultures of B. aerogenes in sputum and blood.

The patient was placed in an oxygen tent, given intravenous glucose solution and intramuscular penicillin 120,000 units immediately and 40,000 units every three hours thereafter. This was supplemented for seven days with sulfadiazine 0.5 Gm. every four hours and sulfamerazine 0.5 Gm. every eight hours by mouth. He was maintained on digitalis 0.1 Gm. daily. The patient's temperature was normal by the third hospital day (Fig. 1), but on the seventh day spikes to 100.5°F. began to appear. On the tenth day the patient had a severe shaking chill and the temperature was found to be 104.5°F. and the white blood cell count 20,300 per cu. mm. Bronchial breath sounds



2A 2B

FIG. 2. A, Case III, chest film on admission to the hospital with pneumococcic pneumonia; B, chest film showing spread of pneumonic infiltration, especially in right lung field at the time of clinical relapse due to B. aerogenes.

were heard throughout most of both lung fields. (Fig. 2B.) Since this episode was thought to be due to a new invading organism, streptomycin 0.2 Gm. every three hours was added to the penicillin injections. Cultures of the nose, throat and blood all yielded growth of Bact. aerogenes, the former two sources also containing small numbers of Staphylococcus albus. The patient's temperature dropped promptly and then slowly reached a normal level by the sixteenth day. The patient's subsequent course was long but uncomplicated. During this time his appetite and sense of well being improved, signs and x-ray evidence of pulmonary consolidation regressed and on the twenty-sixth day cultures of the throat grew only alpha streptococci. Follow-up films three months later still showed marked fibrosis at the site of his previous pneumonia.

*Comment.* An elderly man with emphysema, chronic bronchitis, probable bronchiectasis and a history of recurrent pulmonary infections of ten years' duration contracted pneumococcal pneumonia which responded clinically and bacteriologically to penicillin therapy. On the tenth day of penicillin treatment, however, he developed evidence of blood stream and pulmonary re-infection due to Bact. aerogenes. A high index of suspicion and the prompt addition of streptomycin to the therapeutic regimen resulted in rapid regression of the pneumonic process and recovery from infection.

CASE IV. R. W. (No. M6527), a twenty-two year old colored man was admitted to the hospital for the ninth time on March 5, 1948. The patient had been followed since childhood at the Children's Hospital and more recently at the Peter Bent Brigham Hospital for sickle-cell anemia. There had been multiple admissions for hemolytic crises. In 1941 the patient was hospitalized for a pneumococcus, type III pneumonia of the left lower lobe which was successfully treated with sulfathiazole. For four days before the present admission the patient had a sore throat with mild cough and on the day of entry he developed fever, some shortness of breath and pain in the left anterior chest.

Examination revealed a thin, acutely ill colored boy in moderate respiratory distress. The temperature was 102.4°F. (56.9°C), pulse 104, and blood pressure 118/64 mm. Hg. There were many bronchial rales and slightly diminished breath sounds at the left base and axilla. The heart was enlarged with a rapid regular

rate and a grade II systolic apical murmur. The spleen was not palpable and the remainder of the examination was not remarkable.

The blood Hinton test was negative. The urine showed 1+ protein and occasional white blood cells. Hemoglobin was 10 Gm. per cent, hematocrit 30 per cent and the white blood cell count 26,000 with 88 per cent neutrophiles and many sickle forms on smear. Except for a bilirubin of 5.0 mg. per cent blood chemical values were normal. Stool guaiac was negative. On admission a sputum culture yielded a heavy growth of Diplococcus pneumoniae with a few Hemophilus influenzae and Neisseria catarrhalis. X-ray of the chest revealed a triangular area of consolidation at the left base.

Within twelve hours after treatment with penicillin, 50,000 units intramuscularly every three hours, the temperature was normal. Within twenty-four hours, however, the patient had a chill and the temperature rose to 103.6°F. The white blood cell count was 28,000 per cu. mm. and physical and x-ray examination revealed a spread of the area of consolidation in the left lower lobe. An immediate gram-stained smear of the throat and sputum showed predominance of gram-negative rods. On culture these were identified as H. influenzae. A few colonies of beta hemolytic streptococci were also cultured. Streptomycin, 175 mg. every three hours, or 1.4 Gm. per day, was given in addition to penicillin therapy, and during the next five days the temperature gradually dropped to normal. Sputum culture on the eighth day grew no H. influenzae. After fifteen days of such combined chemotherapy the lungs cleared considerably and at the time of discharge on the twenty-second hospital day the patient was well.

*Comment.* A young colored man with long-standing sickle-cell anemia developed pneumonia with an initial sputum culture containing many pneumococci and a few H. influenzae. Following twelve hours of penicillin therapy the patient improved. On the second day, however, pneumonic infiltration extended, coincident with the appearance in the sputum of H. influenzae in large numbers. No pneumococci were recovered at this time. Streptomycin treatment was instituted at the time of clinical relapse on the basis of the gram-stained smears of the throat and sputum which showed an abundance of small gram-negative rods. After discontinuation of combined therapy cultures no longer contained either D. pneumoniae or H. influenzae.

## OBSERVATION

Four case histories are presented which demonstrate clearly the importance of following shifts in bacterial flora of certain patients during specific antibiotic therapy. Two of the patients came to autopsy and were found to have extensive bronchopneumonia due to gram-negative organisms. Each of them had received prophylactic and postoperative penicillin for gastrointestinal surgery. The third patient was first treated for pneumococcus pneumonia superimposed upon extensive chronic pulmonary disease. Penicillin therapy cleared the pneumococcus infection but was promptly followed by recurrence of pneumonia and septicemia due to B. aerogenes. This infection was brought under control by streptomycin. In the fourth patient pneumococcus pneumonia responded to penicillin but was followed by a relapse of pneumonia due to H. influenzae. The latter organism had been present in the initial cultures before penicillin therapy. The H. influenzae infection was successfully treated with streptomycin.

Each of these patients had underlying poor resistance to disease. The two surgical patients were complicated problems in which chemotherapy was only one of many factors involved in their course. It is fair to say that pneumonia due to B. coli or proteus occurring in these patients is an uncommon surgical complication unless this type of organism has previously been established in the respiratory tract. Since neither patient had obvious chronic bronchitis or chronic sinusitis, the most common precursors for such gram-negative infections, it is likely that suppression of the normal gram-positive respiratory bacterial flora by penicillin was the immediate reason for the unhampered growth of coliform organisms. It is unknown whether these organisms

arrived via the blood stream, lymphatics or through regurgitation. The fact is that the patients died of overwhelming bacterial pneumonia due to these organisms.

In the last two patients, both medical problems, there was again a poor natural resistance to infection. Each had previously had many and varied acute respiratory illnesses. The justified use of penicillin for the first infection did not relieve us of the likelihood of secondary infection. In these patients accurate knowledge of the immediate status of the bacterial flora was most easily obtained by studying gram stains of sputum specimens. Prompt changing of therapy when the flora shifted was made possible by information gained in this way.

In the light of experiences herein reported it is apparent that marked adverse shifts in the bacterial flora of a viscus may be induced by powerful chemotherapeutic agents. Such adverse shifts are most likely in debilitated persons undergoing various surgical procedures or in patients with underlying poor resistance to infection as evidenced by low serum proteins, quite low white blood counts or the presence of chronic foci of infection. These untoward alterations in flora may lead to overwhelming infections within the time required for ordinary cultures to grow in the laboratory. Therefore, frequent gram-stained smears of body secretions are invaluable in following shifts from gram-positive to gram-negative organisms or in ascertaining predominating morphologic bacterial cell types.

The routine use of combined penicillin and streptomycin from the start of serious respiratory infections or the use of sulfadiazine alone because it is effective against many organisms of the gram-negative as well as the gram-positive group is not recommended. It has been pointed out that this biologic complication of penicillin therapy is unusual. It does not justify exposing the majority of persons treated with penicillin to the well known hazards of streptomycin therapy when penicillin alone is most often quite adequate. A more subtle pitfall of such methods is not so much that specific infecting organisms are not recognized but rather that attention is directed entirely toward the bacteria-chemotherapy aspects of an illness and critical host factors are not fully evaluated. Neither is the use of sulfadiazine alone a safe refuge from accurate diagnosis. It is not as effective as penicillin against some organisms, for example staphylococcus, and it is powerless against others such as the influenza bacillus. Unfortunately it is just these organisms which are secondary invaders when host resistance is low and penicillin has altered the bacterial flora. The technical burden of frequent gram-stained smears of body secretions in such acute illnesses is no greater than taking an x-ray and it will usually yield equally valuable information when planning specific treatment.

Until the introduction of penicillin into therapy, specific chemotherapy was plagued with reasons enough for accuracy in diagnosis. A lack of clinical response could be due to an incorrect diagnosis, to inadequate dosage, to a resistant organism, to a walled-off infection, to a drug reaction. Now penicillin has added still another "drug reaction," namely, the shift in bacterial flora. This problem seems to have arisen out of the sheer effectiveness and specificity of the chemotherapeutic agent itself.

SUMMARY

1. Four recent case histories from the Peter Bent Brigham Hospital are presented in which penicillin therapy was followed by complicating pneumonia due to gram-negative organisms. Two patients, treated prophylactically during and following surgery of the gastrointestinal tract, died. Two other patients, successfully treated for pneumococcal pneumonia, developed a secondary pneumonia due to gram-negative organisms. Recovery followed prompt institution of streptomycin therapy.

2. The importance of previous chronic pulmonary disease, of general debility and of the presence of a mixed gram-positive and gram-negative flora in the cultures of

the respiratory tract before treatment is stressed in the pathogenesis of this type of infectious complication.

3. The simple gram-stained smear of the throat or sputum at the time of the sudden chill and rise in temperature during chemotherapy may permit an immediate diagnosis and prompt institution of proper drug therapy.

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# Aureomycin in the Treatment of Tularemia*

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THE effectiveness of aureomycin in therapy of brucellosis and rickettsioses[1–5] suggests that it might also be useful in tularemia, since in many respects B. tularense occupies a position intermediate between brucella and rickettsiae and has properties in common with both. The low toxicity of aureomycin and its activity when administered orally would offer decided advantages should it prove efficacious in the treatment of tularemia.

Aureomycin has been shown to exert a bacteriostatic effect against B. tularense *in vitro*[6] and to possess striking suppressive power against tularemia in mice although most of the animals died after cessation of treatment.[6,7] Complete protection was achieved against only small inocula. Experimental tularemia in the mouse is a fulminating infection with 100 per cent mortality and it is difficult to apply these results to the human disease. Woodward et al.[7] have recently reported on three patients in whom aureomycin therapy was considered effective. Our results with aureomycin treatment of three patients with tularemia at Lawson Veterans Administration Hospital and Grady Memorial Hospital are described herein.

## CASE REPORTS

CASE 1. *Tularemic pneumonia:* A thirty-seven year old Negro skinned and dressed two wild rabbits on December 4, 1948. On December 9th he noted malaise followed by a shaking chill, generalized aching and headache. The following day his temperature was 102°F. Fever continued and he remained in bed. On December 13th, the fifth day of illness, he was admitted to Lawson Veterans Administration Hospital.

The patient appeared moderately ill. He was oriented but lethargic. Oral temperature was 99.6°F., pulse rate 74, respiratory rate 24 and blood pressure 100/70. There was a crusted ulceration measuring 3 mm. in diameter over the dorsal surface of the distal interphalangeal joint of the left thumb. No surrounding tenderness, erythema or edema were present. This lesion had been present since mild trauma three weeks previously. Non-tender, firm lymph nodes measuring about 1 and 1.5 cm. were palpable in the left and right axillae, respectively. Except for occasional non-productive cough, examination of the chest was negative and the rest of the physical examination was non-contributory.

Examination of the blood on the sixth day of illness revealed 7,950 leukocytes per mm.$^3$ of which 88 per cent were neutrophiles. The urine had a specific gravity of 1030; it contained no sugar and 3+ albumin. An uncentrifuged specimen showed 3 to 6 red cells, 5 to 10 white cells and a few granular casts per high power field.

On the sixth day of disease the temperature rose to 105°F. and the respiratory rate to 32. (Fig. 1.) Cough became more frequent and the patient appeared seriously ill. Although physical examination of the chest was negative, x-ray showed confluent patchy consolidation in the peripheral portion of the right upper lung field with extensive right hilar lymphadenopathy. (Fig. 2A.) The sputum smear and culture revealed only normal bacterial flora; culture for tubercle bacilli was later reported negative. Three blood cultures in tryptose phosphate broth were negative December 14th and 15th.

The presence of pneumonia associated with a history of rabbit contact suggested the diag-

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nosis of tularemia although the lesion on the left thumb appeared purely traumatic and there was no significant peripheral lymphadenopathy. The temperature followed a typhoidal course ranging from 103° to 105°F. without remission. On the seventh day of illness oral administration of aureomycin* was begun in doses of 1.5 Gm. every six hours for four doses, then 1 Gm. every six hours. Within twenty-four hours the temperature declined to 99.8°F. but rose again to 101°F. then dropped to 99.2°F. on the ninth day of disease. The respiratory rate fell to 20, the cough decreased and the patient was greatly improved. Although he continued to feel well except for residual weakness, the fever then began to increase daily. On the twelfth day of illness the aureomycin dosage was increased to 1.5 Gm. every six hours but the temperature continued to climb reaching 103.2°F. on the fourteenth day. The patient did not appear very ill; his cough had almost subsided. The chest remained clear to physical examination and there was little change noted in the x-ray. The leukocyte count was 4,400 per mm.[3] Aureomycin was discontinued after a total dosage of 35 Gm. Within forty-eight hours the temperature dropped to normal.

The agglutination test with B. tularense antigen was negative on the sixth day of illness but became positive in dilutions of 1:1280 on the fourteenth day and 1:2560 on the sixteenth day. Repeated agglutination tests with Br. abortus antigen were negative.

The patient continued afebrile and improved steadily. Chest x-ray on the twenty-second day (Fig. 2B) showed considerable clearing of the pulmonary consolidation and reduction in the hilar lymphadenopathy. During the fourth week convalescence was complicated by urinary obstruction resulting from an old stricture of the posterior urethra. A urine culture on the twenty-sixth day (twelve days after discontinuation of aureomycin) yielded beta hemolytic streptococci and coagulase positive staphylococci. The stricture was dilated on the twenty-eighth day, followed by a brief febrile rise to 100°F. Urinary symptoms were relieved and the patient was discharged on January 8, the thirty-first day of illness.

The possibility that the fever on the fourth to eighth days of aureomycin therapy might have been caused by a drug reaction was considered and the patient was readmitted on January 31st. Since discharge he had felt well except for residual weakness, slight exertional dyspnea and occasional cough. Physical examination was essentially negative. The serum

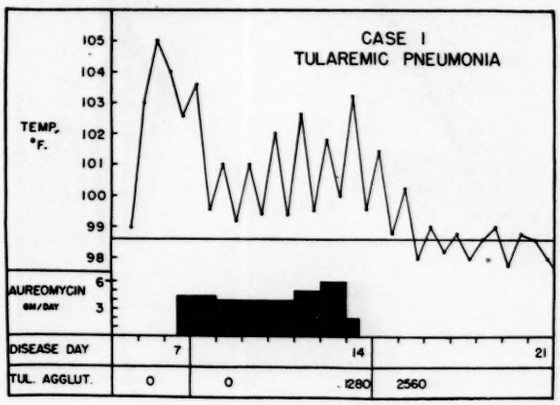



FIG. 1.

agglutinated B. tularense antigen in a dilution of 1:640. The urine was negative except for 2 to 5 white blood cells per high power field in an uncentrifuged specimen. Further dilatation of the urethral stricture was not required. Chest x-ray on February 1st showed only a few delicate linear densities in the base of the right upper lobe. (Fig. 2C.) The right hilar shadow remained somewhat enlarged.

A cautious trial course of aureomycin was given beginning on January 31st with a dosage of 0.25 Gm. orally every six hours. On February 3rd the dosage was increased to 0.25 Gm. every four hours and continued until February 7th. A total of 9 Gm. was given. The patient had no symptoms and the maximum oral temperatures were 99°F. and 99.2°F. Although the dosage was smaller than that previously given for treatment, there was no evidence that the secondary rise of temperature at that time was due to sensitivity to aureomycin. The patient was well when discharged from the hospital on February 9th.

CASE II. *Ulceroglandular tularemia:* A thirty-three year old Negro cut his left index finger with a pocket knife about November 18, 1948. On November 20th he ate rabbit but denied handling the animal before it was cooked. His illness began abruptly on November 23rd with headache and fever, followed shortly by a shaking chill. A few hours later a second chill occurred. Next day anorexia, nausea and vomiting appeared with another chill and severe head-

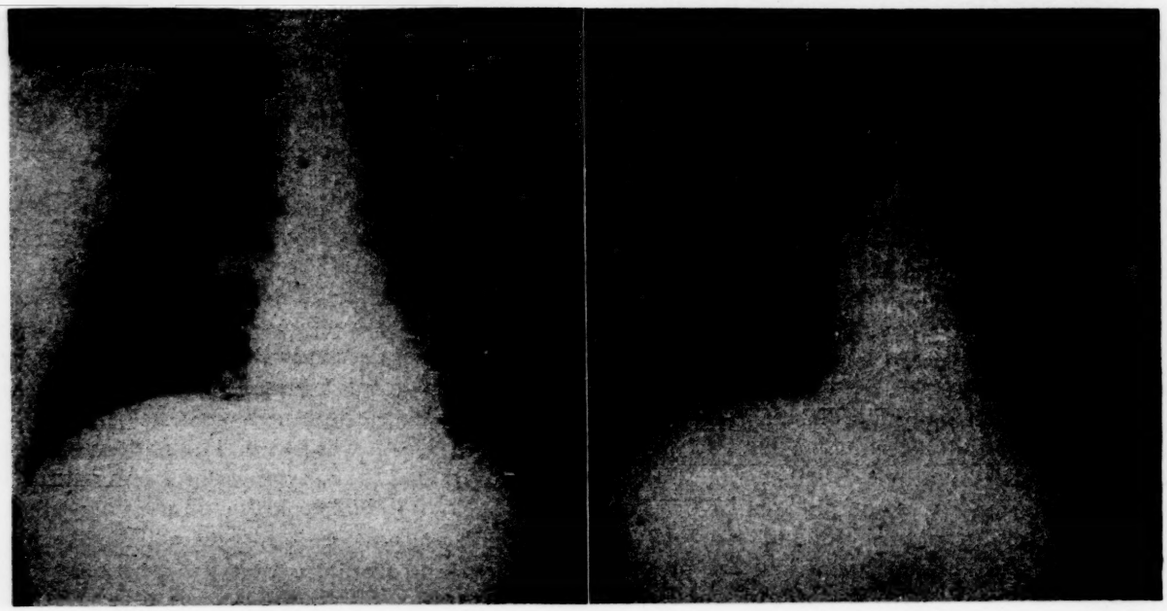
* The aureomycin used in treatment of the patients reported herein was supplied by courtesy of the Lederle Laboratories Division, American Cyanamid Co.

FIG. 2A. Case I, sixth day of disease.

finger there was a crusted ulcer measuring 1 by 2 cm. without surrounding induration or tenderness. A firm tender node 2 cm. in diameter was palpable in the left axilla. Except for dental caries the remainder of the physical examination was non-contributory.

Examination of the blood revealed 19,800 leukocytes per mm.$^3$ with 65 per cent neutrophiles. The urine had a specific gravity of 1024; it contained no sugar and 2+ albumin. A centrifuged specimen showed occasional red cells and 5 to 7 white cells per high power field. Chest x-ray was negative. Two blood cultures in tryptose phosphate broth on the fourteenth day of illness and two on the fifteenth day showed no growth. Serum agglutinins for B. tularense were present in a titer of 1:80 on the fifteenth day and 1:160 on the sixteenth day.

During the first forty-eight hours in the hospital the fever followed a septic course (Fig. 3), reaching a peak of 104.2°F. on the



2B 2C

FIG. 2. B, Case I, twenty-second day of disease; C, Case I, fifty-fifth day of disease.

ache. He remained at home, and fever, weakness, aching, anorexia and occasional nausea and vomiting continued. An infected ulcer developed on the finger at the laceration site and a tender swelling appeared in the left axilla. He was admitted to Grady Memorial Hospital on December 6, the fourteenth day of illness.

The patient was acutely ill. Oral temperature was 102°F., pulse rate 112, respiratory rate 20 and blood pressure 120/80. On the left index

sixteenth day of illness. Aureomycin was started orally at that time in doses of 1.5 Gm. every six hours and administered in lesser doses as shown in Figure 3 until the twenty-third day. A total of 19.5 Gm. was given.

A remarkable clinical improvement occurred after the start of aureomycin therapy. Within twelve hours the temperature dropped to normal and did not rise above 99.4°F. thereafter. Coincident with the fall in temperature

there was profuse perspiration and striking subsidence of symptoms. Malaise and aching disappeared, the appetite returned and strength was rapidly regained. Serum agglutinins for B. tularense rose to 1:320 on the seventeenth day and were present in a dilution of 1:640 on the twenty-first, twenty-fourth and twenty-seventh days. On the twenty-seventh day the agglutinin titer for Br. abortus was 1:160. The patient was allowed out of bed on the eighteenth day and was increasingly ambulatory thereafter. The finger ulcer healed in a few days. By the twenty-fourth day the axillary node had decreased to half its original size and the patient was discharged on December 21st, the twenty-eighth day of disease. When he was seen in the outpatient clinic on January 7th, the axillary node was no longer palpable and he appeared completely recovered.

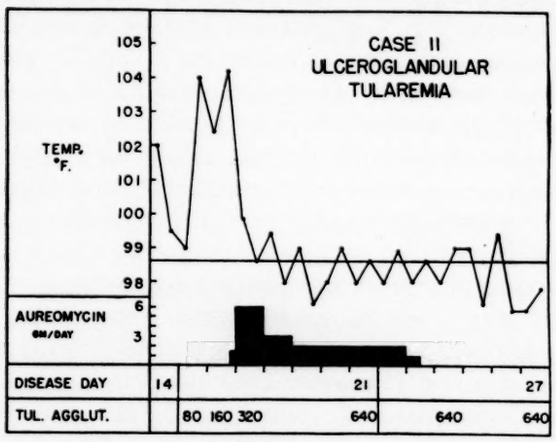



FIG. 3.

CASE III. *Ulceroglandular tularemia:* A forty-four year old Negro incurred an abrasion of the right index finger while hunting on November 23rd. He killed and dressed five wild rabbits. The injured finger became painful on November 26th and he developed headache, malaise and chilly sensations. Next day he was much worse and remained in bed. After three or four days the finger lesion drained a small amount of pus and a tender swelling appeared in the right axilla. Five or 6 days later there was some improvement and he was ambulatory although weakness, malaise and low-grade fever persisted until admission to Grady Memorial Hospital on December 8th, the thirteenth day of illness.

The patient's wife, who prepared and cooked the rabbits, also developed ulceroglandular tularemia on November 26th. She was extremely ill and was admitted to the hospital several days before her husband. Streptomycin therapy was given and she recovered after a stormy course although incision and drainage of a huge fluctuant axillary abscess was necessary.

On admission the patient was only mildly ill. Oral temperature was 101.2°F., pulse rate 84, respiratory rate 22 and blood pressure 115/70. On the right index finger there was an indolent lesion measuring 1.5 by 1 cm. which was slightly elevated and indurated and covered by scaly epidermis. A tender non-fluctuant lymph node measuring 5 cm. in diameter was palpable in the right axilla. No other significant findings were noted.

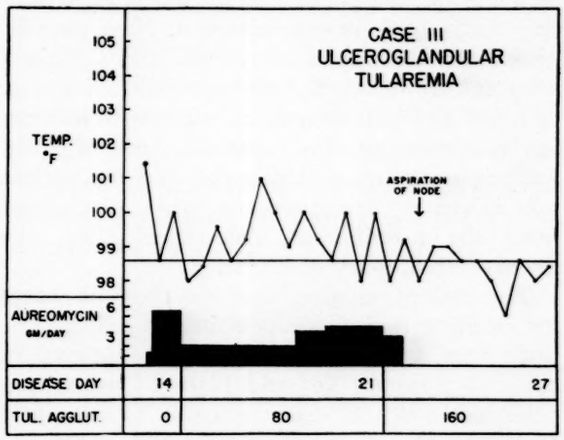



FIG. 4.

The leukocyte count was 21,550 per mm.$^3$ with 74 per cent neutrophiles. Urinalysis was negative except for occasional white cells in a centrifuged specimen. Agglutination tests with B. tularense antigen were negative on the thirteenth and fourteenth days of illness. Chest x-ray was negative on the thirteenth and twenty-first days.

In view of the history and clinical picture and since the patient's wife had unquestionable tularemia, a diagnosis of ulceroglandular tularemia was made. Aureomycin was started orally late on the thirteenth day of illness in dosage of 1.5 Gm. every six hours for four doses after which the dosage was reduced and continued as shown in Figure 4. Within twenty-four hours after the start of therapy the patient felt better and in forty-eight hours the temperature dropped to normal. He was asymptomatic except for tenderness in the axilla. However, on the sixteenth day of illness the temperature rose to 99.4°F. and on the seventeenth day to 101°F. Serum agglutinins for B. tularense ap-

peared in a titer of 1:80 on the eighteenth day. On the nineteenth day aureomycin was increased to 1 Gm. every six hours; but since the axillary node remained tender and gradually became fluctuant, the antibiotic was discontinued on the twenty-second day. Aspiration of the node was performed on the twenty-third day and 10 ml. of pus removed. Next day the temperature dropped to normal and remained so. Agglutinins for B. tularense reached a titer of 1:160 on the twenty-fourth day, with no cross agglutination of Br. abortus antigen. The axillary node was still palpable but the patient was otherwise asymptomatic when discharged from the hospital on December 22nd, the twenty-seventh day of illness.

The patient remained free of symptoms except for swelling and tenderness in the axilla. The node was again aspirated in the out-patient clinic on January 4th and 11th, 15 ml. of pus being removed on each occasion. On January 15th, the fifty-first day of illness, spontaneous rupture occurred after which drainage gradually subsided. By February 1st, sixty-eight days after onset, all induration in the axilla had disappeared and the patient was entirely well.

## COMMENT

Streptomycin was the first chemotherapeutic agent shown to influence tularemic infection significantly in experimental animals.[8] Aureomycin is the second substance reported to exert similar activity.[6,7] Woodward et al.[7] compared the action of the two antibiotics against tularemia in mice and concluded that aureomycin was more effective than streptomycin in delaying death. Three tularemia patients treated by these authors with aureomycin appeared to respond well, and evaluation in additional cases is desirable.

The course of human tularemia is notoriously variable, ranging from mild subclinical infections to overwhelming septicemia with death in a few days. Even without specific therapy the mortality in 19,208 reported cases of all types was only 7.4 per cent.[9] The possible pitfalls in assessing therapeutic effect against this disease have been amply demonstrated over the last twenty years by passing enthusiasms for various drugs and other agents. It is therefore unsound to draw conclusions from the results of treatment in a few cases.

The uncomplicated ulceroglandular form of the disease is especially unsuited for therapeutic trials since the mortality is exceedingly low and the febrile course unpredictable. Suppuration and drainage of the involved nodes occur in about 50 per cent of cases.[10] In the remainder there is gradual healing over a period of several weeks or months. When given to acutely ill patients with ulceroglandular tularemia, streptomycin usually produces prompt improvement in general symptoms with decrease of temperature to normal in three to six days, but its value in the treatment of glandular involvement is much less certain. Berson and Harwell[11] concluded that streptomycin had little effect upon such glands when given after the twelfth day of disease.

As pointed out by Francis,[9] the more severe pulmonary form of tularemia provides a better test of a chemotherapeutic agent; it was in treatment of such patients that the value of streptomycin was firmly established. Streptomycin has reduced the mortality of tularemic pneumonia from about 40 per cent[12] to a very low figure.[9,11,13] It produces striking relief of symptoms in twenty-four to forty-eight hours and in most cases the temperature falls to normal within three to seven days. Several weeks may be required for complete clearing of pulmonary lesions as seen on x-ray.

Aureomycin treatment was followed in all three patients presented herein by definite subjective improvement and a drop in temperature within twenty-four hours after starting therapy. At the end of forty-eight hours in all three cases the temperature approached normal levels. In Case 1, however, the temperature gradually rose during the next five days to 103.2°F. and fell to normal only forty-eight hours after discontinuation of therapy. Nevertheless the patient showed striking subjective and objective improvement, and the pneumonic process resolved much more quickly than would have been expected without specific therapy. There was no pleural effusion.

This patient's condition was complicated by a urethral stricture and low-grade urinary tract infection.

Case II was an uncomplicated case of ulceroglandular tularemia in which the patient was acutely ill on the sixteenth day when aureomycin treatment was started. Striking improvement occurred within twelve hours. Although the probable course of such a case could not be predicted, it would be most unusual to see such rapid subsidence of fever and symptoms without specific therapy.

Case III was a mildly ill patient with ulceroglandular tularemia in whom aureomycin therapy was started on the thirteenth day of illness. Subjective improvement and an initial fall in temperature occurred but later he ran a low-grade fever despite continued therapy. Aureomycin obviously had no effect upon the axillary node which became fluctuant during therapy and required aspiration on three occasions. Healing finally occurred after spontaneous rupture and drainage of the gland on the fifty-first day of disease.

No significant toxic reaction occurred in these patients during or after aureomycin treatment. Although drug fever was suspected in Case I, readministration of the antibiotic failed to produce a febrile reaction. In Case III there was slight stimulation of bowel action resulting in two to three soft stools daily during aureomycin therapy. This patient also showed 1 to 2+ albuminuria on the fifth to seventh days of therapy. Centrifuged urine specimens contained 1 to 5 red cells and 1 to 5 white cells per high power field, with an occasional white cell cast. Urinalyses at two-day intervals revealed no further albuminuria and the cellular elements rapidly disappeared. There were no significant blood changes and none of the patients complained of anorexia, nausea or vomiting.

Although it is difficult to predict the course of tularemia without specific therapy in individual cases, we believe that two of our patients (Cases I and II) were impressively benefited by aureomycin. Certainly aureomycin exerted no action on glandular suppuration in Case III but streptomycin has also failed in similar cases. Our results and those of Woodward et al.[7] encourage further trial of aureomycin in human tularemia. At present the optimal dosage and duration of treatment are unknown, and available data are insufficient to permit a sound clinical comparison with streptomycin in the treatment of this disease. Proper evaluation of aureomycin will not be possible until more patients have been treated, including a number of cases with pulmonary involvement.

## SUMMARY

1. A patient with tularemic pneumonia and one with ulceroglandular tularemia improved strikingly after oral aureomycin therapy and recovered rapidly.

2. Another patient with ulceroglandular tularemia treated on the twelfth day of illness improved subjectively but aureomycin did not prevent glandular suppuration.

3. Further evaluation of aureomycin in human tularemia is indicated.

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# Review

# Newer Concepts of the Role of Potassium in Disease*

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Within the last few years a considerable amount of new data has been accumulated on potassium, one of the chief cations in the body. Much of this has been based on balance studies and as such represents a fundamental contribution to our knowledge of this electrolyte in various physiologic and clinical situations. Nonetheless, there is still no adequate explanation of how or why tissue cells acquire and maintain concentrations of potassium in excess of those in interstitial fluid and serum. Even though the mechanism of this unequal distribution remains a challenge, the newer findings identify factors which influence concentrations and total amounts of body potassium. Their importance can perhaps be best emphasized by presentation against the background of previous knowledge and beliefs.

## EXTRACELLULAR POTASSIUM

*Hyperpotassemia, Its Origin and Significance.* It has been known that under ordinary conditions the potassium levels in extracellular fluid vary to only a limited extent. In a healthy fasting individual the upper limit of this range is about 5.5 mEq./L. In certain instances this may be exceeded and not necessarily indicate any abnormality. Thus ingestion of potassium salts can increase, temporarily at least, serum concentrations of this ion above 5.5 mEq./L.[1] High serum levels have also been observed in the course of potassium balance studies conducted in diabetic and non-diabetic subjects.[2,3] Such increments of potassium in the extracellular fluid are soon eliminated by the kidneys in those subjects whose body stores of this cation are intact. The extra potassium may be excreted immediately or it may enter certain cells, such as those of the liver or muscle, for a temporary sojourn. In a matter of hours this portion of the administered potassium re-enters the interstitial fluid and is in turn excreted by the nephrons.[4] Recent work has shown that two mechanisms exist whereby this may be accomplished. Not only, as previously recognized, is potassium removed by glomerular filtration but under certain circumstances excretion through the renal tubules can be unequivocally demonstrated.[5,6]

The processes whereby undue and dangerous rises in extracellular potassium can be mitigated or prevented may prove inadequate under some conditions. It is possible, for example, to inject potassium rapidly enough by vein to produce toxic concentrations in serum, overtaxing the physiologic adjustments which have been described to these extra supplies of the cation.[7] On the other hand, similar degrees of hyperpotassemia may be observed in disease states with usual or even limited intakes of potassium. These rises may result from the following, alone or in combination: (1) contraction of the volume of extracellular fluid, (2) inability of the cells to take up potassium, (3) transfers of cell potassium to the extracellular compartment and (4) inadequate renal excretion. All these factors,

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with the possible exception of (3), may be operative for example in producing the hyperkalemia of untreated adrenal cortical insufficiency.[8] The role of these various processes in renal insufficiency remains unsettled. As a matter of fact, until recently it has appeared as if potassium intoxication in renal failure occurred only in subjects with complete suppression of urine formation. This belief has been based on the readiness with which experimental animals with anuria following bilateral nephrectomy or ureteral ligation died of potassium poisoning.[9] Similar occurrences were thought to be rare in patients with terminal chronic nephritis, presumably either because failing kidneys still excreted potassium or because cells of the body failed to release, or even took up potassium.[10] Recent studies have indicated, however, that potassium poisoning can be demonstrated in a minority of such patients if they are kept under constant surveillance up to the moment of death.[11] These findings did not appear to be agonal since serial observations revealed the gradual evolution of the changes known to occur with potassium intoxication. These were succinctly described in 1938 by Winkler, Hoff and Smith in experimental studies on dogs.[12] In the most characteristic form the electrocardiogram changed progressively as the serum potassium level rose. In the initial phases the T wave increased in height. This was followed by broadening of the QRS complex with loss of the ordinary contours, changes in the S-T and T segments and disappearance of the P wave. Ultimately the heart stopped in diastole. In observations on humans an increase in the height and a sharpening of the contour of the T waves were also the earliest changes detectable as the potassium concentration in serum rose; subsequent heart block has been observed as well.[11]

To date, therefore, poisoning due to increased levels of extracellular potassium appears to be a problem only in patients who are receiving this cation in undue amounts or in a minority of those with renal failure. The potassium levels in untreated Addison's disease usually do not attain the lethal range. It is possible, however, that in agonal states in these subjects and in others potassium in extracellular fluid rises to toxic concentrations. This is logical in view of the marked increase found at postmortem. This would suggest that with impending death and disruption of the ordinary physiologic barriers which restrain cell potassium from pouring out into extracellular fluid this change may appear premortem.

*Occurrence and Effects of Hypopotassemia.* In contrast to hyperkalemia decreased levels of serum potassium have been recorded under a great variety of clinical conditions. The lower limit of normal in adults appears to be about 3.5 mEq./L. Abnormally low levels of extracellular potassium can, on theoretical grounds, result from: (1) dilution by low potassium fluids, (2) losses of the cation in urine or other body fluids or (3) transfers of potassium into cells. Obviously an inadequate intake of potassium will maintain the low concentrations produced by these aforementioned processes.

All of these factors may be operative in the development of low serum potassium levels during recovery from diabetic acidosis and coma.[2,13] Such patients usually develop anorexia and vomiting during the early phases of their illness.[14] As a consequence the intake of potassium is reduced essentially to zero. At the same time considerable amounts of potassium are lost in the gastric secretions and in the urine.[15–17] Even though the body stores of this electrolyte are considerably depleted in these various ways, the patients are frequently admitted with elevated or normal concentrations of potassium in serum.[2,13,18] This is explicable, in part at least, by the attendant contraction of the plasma and extracellular volumes as a result of dehydration. With administration of large amounts of potassium-free fluids, such as saline and subsequently glucose solutions, the volume of body water is reexpanded. At the same time potassium moves into cells under the impetus of insulin, restoration of carbohydrate catabo-

lism, glycogen deposition and protein formation. While these processes are going on, further amounts of potassium are lost in the urine. The magnitude of these losses tends to diminish, however, during convalescence until in some instances urine:plasma potassium ratios lower than 1.0 are encountered.[19] As a consequence of these various factors hypopotassemia develops in almost all patients during the early phases of the hitherto standard treatment of diabetic acidosis with parenteral fluids.

Balance studies similar to those conducted in diabetic acidosis and coma have served to define, in part, the chain of events which results in low serum potassium values in infants with pyloric obstruction and prolonged vomiting.[3,20] Although actual measurements during the prehospitalization phase of such subjects are not available, it seems highly probable that the loss of potassium in vomitus is of considerable magnitude. This is, of course, accompanied by a greatly reduced intake of potassium in food. On admission these patients are frequently found to have hypopotassemia in addition to hypochloremia, high serum bicarbonate levels and deficits of body water. It is true that at the time of admission, or shortly thereafter, losses of potassium in the urine are quite low.[3,19] This does not exclude the possibility that earlier losses via this route were of greater magnitude. The usual therapy with low potassium fluids, while oral feedings are withheld, either produces or further aggravates hypopotassemia.

Some of these same mechanisms account for the low serum potassium values found in many adult subjects with gastrointestinal disorders.[21,22] Again the combination of starvation and electrolyte losses in gastric or intestinal secretions is present. Such individuals, in contrast to the infants just described, continue to lose considerable amounts of potassium in the urine. Frequently the losses via this route exceeds those in vomitus. Replacement therapy has heretofore not included the use of fluids which contain adequate amounts of potassium. When abnormally low levels of serum potassium develop in such subjects, they are usually referable to a combination of these factors. Renal losses, however, appear to play a predominant role.

Similarly, although confirmatory studies are lacking, it is by inference continued and perhaps excessive renal loss that is responsible for the low serum potassium values seen, surprisingly enough in view of the earlier discussion, in certain patients with renal disorders.[22–25] These may represent instances in which the glomerular filtration of potassium is well maintained while tubular reabsorption is considerably impaired. Unfortunately complete and prolonged balance studies are not available in the cases cited and hence no statement is possible as to the role of inanition, vomiting and fluid administration which frequently accompany renal failure. Similar decreases in the potassium level can be produced, of course, by peritoneal lavage, intestinal perfusion or by means of the artificial kidney using fluid low in potassium.

Up to this time only one category of potassium disorders has been identified in which the decline in extracellular concentration is entirely or almost entirely explicable by a transfer into cells. This is true of periodic paralysis in which serum potassium falls abruptly, concomitant with a *decreased* urinary loss at a time when there is no evidence that extracellular volume has expanded.[26,27] It must result, therefore, from a migration of potassium into cells.

Finally, certain associations must be mentioned since they may represent cause and effect. Thus clinical or experimental alkalosis and hypokalemia are concomitantly observed. This has been described in the alkalosis of Cushing's disease, during DOCA intoxication, in anorexia nervosa and in subjects with chronic losses of gastric secretions. The simultaneous occurrence of these two changes is much too frequent to represent chance and suggests, particularly in view of Darrow's experiments,[32] a more fundamental relationship. However, since in all of these disorders the extracellular

and cell potassium values are apt to be low rather than normal or high, it is obvious that at least the initial decrease occurred through losses in urine or other body fluids. Their continuance can be assigned either to some type of depressant effect of alkalosis on potassium levels or possibly to an inability to replace deficits because of the continued urinary loss of the ion.

The physiologic effects of the low serum and extracellular fluid potassium values appears, insofar as is now known, to be limited to electrocardiographic changes in S-T and T waves and to the occasional production of a reversible and usually non-fatal muscular paralysis. The latter characteristically occurs, by definition, in idiopathic periodic paralysis and is often seen in the other disorders which have been mentioned. The fact that it is not an invariable occurrence emphasizes the need for a flexible concept in predicting the effects of hypopotassemia. This is in accord with what is known of the physiology of this ion. Thus the deposition of protein, of glycogen or continued carbohydrate metabolism will remove potassium from serum and may lower its concentration in the extracellular fluid.[33–35] Since this is not productive of paralysis, it is obvious that a certain range of physiologic variation is present. The degree to which this must be exceeded to produce paralysis apparently differs not only from disease to disease but also from subject to subject.

It is more than probable, therefore, that the chief importance of hypopotassemia lies in the fact that it is frequently associated with deficits of cell potassium rather than that it may produce muscular paralyses or electrocardiographic alterations. It should be emphasized, however, that cell potassium deficits need not be accompanied by hypopotassemia.

## CELLULAR POTASSIUM

*General Considerations.* Thus far the discussion has centered about the potassium present in interstitial fluid and serum. The inaccessibility of the cellular phase of body water for analyses and the difficulties inherent in measuring changes in the composition of cells account for the relative paucity of data concerning intracellular potassium. This is unfortunate because the great bulk of the body stores of this cation is, of course, in cells. The concentrations there are about twenty-fold greater than those in serum. Cell potassium, furthermore, is only partially ionized and hence not all of it is osmotically active. Some is bound to protein in a characteristic ratio to cell nitrogen[33] and some is in all probability combined with phosphate or other complexes. The separate fractions of cell potassium may vary in amount. As cell protein is broken down, for example, potassium bound to this constituent is released to the extracellular fluid.[36] The process is reversed during a period of positive nitrogen balance. In an analogous manner, with water deprivation some of the potassium of cells not associated with protein moves to the interstitial fluid. This, of course, alters the respective osmotic forces and water enters the extracellular phase and mitigates the dehydration there.[37] With rehydration this portion of potassium is reconstituted. Movements of potassium into interstitial fluid, on the other hand, must accompany liver deglycogenation since it is known that during the formation of glycogen, potassium is deposited in a predictable ratio with the polymerized glucose.[34] Potassium also leaves muscle cells during exercise and enters the extracellular pool.[38] This fraction, losing its identity among the general body stores, may then enter the liver and other tissue cells, or it may be excreted in the urine. An obvious corollary to this process must be the re-entry of an equal amount of the cation into the muscle to replenish the original supplies present there. It is also known that the potassium stores in cells can be altered experimentally and clinically under a variety of conditions including dehydration, hypertonicity, oliguria and electrolyte administration.[39] In some but not all of these balance studies evidence was present of a reciprocal exchange of cell

potassium for sodium. Undoubtedly there still are other factors operative which have not as yet been identified or defined.

*Increases in Cell Potassium and Their Apparent Benignity.* Temporary increases in cell potassium following ingestion or injection of potassium salts may be looked upon as a physiologic adjustment. This can be demonstrated readily by following the distribution of administered potassium chloride. The apparent volume of body water through which the ion is dispersed continues to rise until it exceeds the value ordinarily assigned to extracellular fluid and approaches that of total body water. Subsequently potassium leaves the cells and re-enters the interstitial compartment.[4] It is also known, for example, that adrenal cortical insufficiency is associated with increases in the amounts of cell potassium in addition to hyperpotassemia.[40] Experimentally it has been shown that chronic acidosis in non-diabetic animals is accompanied by a slight rise in the content of cell potassium.[32] In periodic paralysis, too, potassium leaves serum and enters cells. Quantitatively these transfers are not necessarily large.[27] For practical purposes these conditions exhaust the known examples of temporary or persistent rises in cell potassium.

It is not possible to state whether or not these increases in cell potassium are in any way harmful. There is no evidence that the temporary penetration of administered potassium ions into cells produces any symptoms. Moreover, as far as is known, none of the clinical manifestations of Addison's disease are explicable on this basis. Such a possibility has not, however, been excluded. The paralytic phase of periodic paralysis appears to be related, as has already been mentioned, to the decrease in extracellular potassium and not to the rise in the intracellular fraction. It may well be that the absence of definite symptoms or manifestations with increases in the total amount of cellular potassium is related to the fact that the concentrations of osmotically active potassium are maintained at a constant. At least two mechanisms exist whereby this adjustment can be made: (1) water can move into the cells in response to osmotic forces whenever the osmotically active portion of this cation increases and (2) potassium which enters the cells may be rendered osmotically and perhaps physiologically inert by becoming bound to anion constituents.[34,41]

To date, depletion of intracellular potassium has been demonstrated by balance studies in a variety of conditions. It has been shown, for example, that during the early phases of the treatment of diabetic acidosis or coma the patients continue to lose potassium from cells.[2,13] To avoid confusion it must be emphasized that this statement refers to the net balance of cell potassium because it is known that with administration of insulin and the resumption of carbohydrate metabolism potassium re-enters cells. These findings must indicate that at that time certain cells are regaining potassium while others are still losing this electrolyte. Losses of cell potassium have also been recorded by Elkinton and his co-workers during the balance studies cited earlier in subjects with gastrointestinal disorders[22] and by Darrow in infants with diarrhea.[42,43] These negative balances of cell potassium were in excess of any losses of this cation which could be attributed to breakdown of cell protein. In all of these conditions any loss of cell potassium to the extracellular compartment must have been accompanied by comparable or greater losses of potassium from the body in urine, vomitus, drainage fluids or excreta. Otherwise the concentration of potassium would have risen to dangerous levels in extracellular fluid. Retention of administered potassium by cells has been observed in these various clinical states as well as in infants convalescent from prolonged vomiting.[3] These findings have been interpreted as indicative of deficits of cell potassium; as already mentioned, injected or ingested potassium salts are not retained to the same degree, if at all, by non-depleted subjects.

It may well be that such extensive losses of cell potassium jeopardize survival. In

experimental studies degenerative changes have been observed in the myocardium following production of deficits of cell potassium by means of a low potassium diet or DCA administration.[44] Moreover, it has been possible to demonstrate by potassium therapy a definitely lowered mortality rate in infant diarrhea. In view of these findings it is not unreasonable to suggest that cellular deficits of potassium may also contribute to the mortality in various other clinical disorders. The actual mechanisms through which these harmful effects are mediated have not been identified. Presumably they are manifestations of interferences with cellular processes as a result of losses of essential constituents. This lack of knowledge by no means minimizes our responsibility in seeking, recognizing, studying and treating potassium deficiency states.

## SUMMARY

An attempt has been made to integrate new findings relevant to potassium metabolism in health and disease with previously known facts. Particular emphasis has been placed on the clinical significance of increments and decrements in the extracellular and cellular fractions of this electrolyte.

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# Seminars on Antibiotics

## Aureomycin in the Treatment of Infectious Diseases*

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In the year which has elapsed since the first published report of aureomycin this new antibiotic has been the subject of widespread interest to the profession and an astonishingly large volume of literature about it, both experimental and clinical, has already appeared in print. Indeed the published data are now so voluminous and the antibiotic so widely used that a general review article seems fully warranted.

Credit for the discovery of this new therapeutic agent goes to Duggar[1] who isolated and described a new species of the Actinomycetes, named by him *Streptomyces aureofaciens*, which possessed the antibiotic properties to be described hereafter. At a certain stage in its growth this microorganism produces the antibiotic substance which is of a faintly golden-yellow color. Preliminary tests demonstrated its activity against a wide bacterial spectrum and warranted the intense efforts of Duggar and his colleagues further to explore its possibilities. Some of its chemical properties have now been described.[2] It is a weakly basic compound containing both nitrogen and non-ionic chlorine. The hydrochloride has an approximate solubility in water of 14 mg./ml. at 25°C., and the pH of the aqueous solution is 2.8–2.9.

*Pharmacology.* Studies of the pharmacologic effect of the drug have been reported by Harned et al.[3] With oral administration mice tolerated 1,500 mg. per kg. and rats 3,000 mg. per kg. The $LD_{50}$ intravenously for mice was 134 mg. per kg., and dogs, cats, rabbits, guinea pigs and mice tolerated intravenous doses of 50 mg. per kg. without symptoms. Chronic toxicity experiments indicated that mice, rats and dogs tolerated oral doses of 100–200 mg. per kg. daily for twelve weeks without ill effects. Generally speaking, no pathologic changes could be determined in any of the viscera studied. No evident effects on cardiac activity, liver function or kidney function (apart from a mild diuretic action) were demonstrable. The drug did not appear to influence vasomotor responses or blood sugar levels and it had no antipyretic effect in rabbits. All in all, these animal experiments indicated the likelihood of a wide margin of safety for human administration; indeed early experiences proved this to be the case.

*Side Effects in Man.* Oral administration of aureomycin is frequently accompanied by nausea and occasionally by vomiting and a metallic taste in the mouth. Females appear more susceptible than males; more than half of the women patients may be quite distressed by these manifestations although their intensity usually diminishes if treatment is continued. The drug also has a slightly laxative action and the passage of an increased number of soft, bulky stools is frequently observed. True diarrhea is extremely rare. It was reported by Lennette et al.[4] that pruritus and soreness of the scrotum occurred in two patients. We have observed three instances of transitory vagi-

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nitis and a small number of cases of glossitis. One questionable instance of drug fever was reported by Collins.[5]

Wright et al.[6] in an early communication described hypochromic anemia accompanying parenteral administration of the drug in a "special diluent." When this diluent was replaced by normal salt the anemia was no longer encountered. It has not been described since nor have there been any published reports of neutropenia. In this clinic, however, one case of complete neutropenia occurred in a dermatologic patient after prolonged administration of aureomycin. Return of the polymorphonuclear leukocytes took place promptly after the drug was stopped, and when it was readministered several weeks later it had no effect on the white blood cells although daily treatment was again given for a long period of time. Toxic effects on the liver, kidney and other organs have not been described.

*Experimental Studies in Vitro.* Aureomycin has a wider range of activity than any other antibiotic thus far discovered, with the possible exception of chloromycetin. It is effective against numerous gram-positive and gram-negative bacteria, all species of pathogenic rickettsiae, several viral agents and possibly certain protozoa.

Crystalline aureomycin hydrochloride is stable in the dry state and will maintain its potency for many months at 20–25°c. In solution, however, it deteriorates more or less rapidly depending upon the pH, the temperature and the composition of the solvent. Unbuffered solutions of the drug in distilled water at pH 2.9 have been maintained at ±4°c. for twenty-three days with no measurable loss of activity, according to Dornbush and Pelcak.[7] However, studies by Chandler and Bliss[8] and by Paine et al.[9] have shown that the drug becomes quite unstable at a neutral or alkaline pH, even at 4°c., and that this instability is increased progressively as the temperature is raised to 37°c. and above. In fact, Bliss and Chandler[10] found that at pH approximately 7.0 about 60 per cent of the activity was lost in eighteen hours at 37°c. while 75 per cent was lost after four hours at 56°c. In addition to progressive loss of activity, Paine et al.[9] demonstrated that the drug is initially less bacteriostatic at an alkaline reaction than it is at an acid reaction—the reverse of what is true for streptomycin. Price et al.[11] and others have found that the bacteriostatic properties of the drug are also adversely affected by many ingredients of culture media such as meat infusion, various peptones, yeast extract, whole blood, fresh or heat-inactivated serum, phosphate buffer and even sodium chloride. These facts must be borne in mind when one attempts to appraise the results of laboratory tests for the *in vitro* sensitivity of bacteria or to evaluate drug levels in blood or other body fluids as determined by different methods.

Generally speaking, *in vitro* tests have shown that aureomycin is somewhat less effective than penicillin against gram-positive bacteria and that its action is approximately the same or somewhat inferior to streptomycin against most gram-negative bacteria. Bliss and Chandler[10] found that strains of Str. hemolyticus, Str. faecalis, D. pneumoniae and Staph. aureus were inhibited by 1.25 μg. or less per ml while E. coli, A. aerogenes and K. pneumoniae required from 1.25 to 5.0 μg. per ml. Similarly, Paine et al.[12] reported that the bacteriostatic concentrations for hemolytic streptococci, pneumococci, gonococci and meningococci did not exceed 1.0 μg. per ml. Most strains of Staph. aureus were inhibited by 1.0–2.0 μg. per ml. although a few strains required up to 12.5 μg. per ml. The gram-negative bacilli—including the typhoid bacillus and other members of the Salmonella group—were somewhat more resistant, their requirements ranging from 3.1 to 25.0 μg. per ml. Unfortunately, nearly all strains of Proteus and Ps. aeruginosa were found to be moderately or markedly resistant to the action of the drug (4.0 to 250 μg. per ml.) although, as shown by Rutenburg and Schweinburg,[13] an occasional strain may be quite sensitive (0.0125 to 0.4 μg. per ml.). It is of considerable

theoretical and practical interest that some strains of Group D streptococci (Str. faecalis) are more sensitive *in vitro* to aureomycin than they are to penicillin.

Bryer et al.[14] reported that strains of Brucella suis were completely inhibited *in vitro* by 0.25 to 0.5 μg. of aureomycin per ml. and Brucella abortus by 0.25 to 2.0 μg. per ml. Spink et al.[15] also found that the drug was active against these species as well as Brucella melitensis both in the experimentally infected chick embryo and in the test tube.

Experiments by Steenken and Wolinsky[16] on the tuberculostatic effect of the drug indicated that growth of a standard laboratory strain of M. tuberculosis, H37Rv, was inhibited by from 2.5 to 40.0 μg. per ml. depending upon the type of fluid medium employed. But the drug failed to modify the course of tuberculous disease in guinea pigs even when given in maximally tolerated dosage.

Price et al.[11] and Chandler and Bliss[8] first pointed out that in tests for bacterial sensitivity the turbidity end points move up during successive days of incubation. This indicates that the drug has primarily a bacteriostatic action although it is also bactericidal in higher concentrations and reflects the progressive deterioration of the antibiotic which was previously mentioned. The effect might also be caused by the emergence of drug-resistant organisms, as is seen so commonly with streptomycin; but these authors, as well as Paine et al.,[12] have demonstrated that resistance to aureomycin is rarely developed by bacteria exposed to aureomycin *in vitro* and that such resistance, when it appears, is usually of a low order. Moreover, no evidence has yet been obtained that resistant organisms elaborate an anti-aureomycin substance or "aureomycinase."

From the standpoint of contemplated therapy it is important to note that bacteria which have developed a marked resistance to either penicillin or streptomycin still retain their native susceptibility to the effects of aureomycin *in vitro*.

*Experimental Studies in Vivo.* The extensive studies which have been made of the therapeutic effects of aureomycin *in vivo* can be only briefly summarized here. In general the results with various bacterial agents conform quite well to what might be predicted from the *in vitro* tests just described. Bryer et al.[17] reported, for example, that aureomycin would satisfactorily protect mice against 10,000 lethal doses of Group A hemolytic streptococci even when relatively small doses were administered either orally or parenterally. Murine infections with type I pneumococci could also be cured, provided larger doses of the drug were given, but little protection was obtained against K. pneumoniae. Little[18] as well as Price et al.[11] found that aureomycin gave poor therapeutic results in mice infected with E. typhosa and other representatives of the Salmonella group; but the latter authors obtained a fairly good effect with a strain of E. coli which was sensitive *in vitro*.

In Brucella abortus infections of mice Heilman[19] found that aureomycin was superior to chloromycetin but that treatment with a combination of aureomycin and dihydrostreptomycin gave the best results. Heilman[20] also reported that aureomycin was highly effective against Borrelia novyi (relapsing fever) and Leptospira icterohemorrhagiae (Weil's disease) in small animals.

Aureomycin was discovered very early to be an astounding curative agent for rickettsial infections in both animals and chick embryos. Wong and Cox[21] showed that the rickettsiae of epidemic typhus, Rocky Mountain spotted fever, scrub typhus, Q fever and rickettsialpox were all extremely sensitive to the drug although, it is important to note, there was no direct effect upon these organisms *in vitro*. Relatively small doses of aureomycin permitted the survival of chick embryos given multiple lethal doses of these rickettsiae, while infections in mice or guinea pigs could be either aborted by early treatment or easily cured after they were clinically established. Anigstein et al.[22] were equally successful in treating epidemic

typhus and Rocky Mountain spotted fever in guinea pigs. Both groups of investigators made the important observation that animals treated at the time of infection or shortly afterward often showed no residual immunity whereas animals treated later in the disease were usually resistant to challenge inoculation with the original organism. This phenomenon indicates that aureomycin—unlike para-aminobenzoic acid—has rickettsiocidal as well as rickettsiostatic properties.

Wong and Cox[21] found aureomycin to have marked therapeutic activity in mice infected either intracerebrally or intraperitoneally with the viruses of psittacosis and lymphogranuloma venereum. Moreover, these viruses did not persist in surviving animals to the same extent as they customarily do when a sulfonamide drug such as sulfadiazine is used as the therapeutic agent. Aureomycin failed to show any therapeutic activity against the following viruses: influenza A and B, canine distemper, rabies, Newcastle disease, Venezuelan equine encephalomyelitis and the MEF-1 strain of poliomyelitis. Experiments with mumps virus in chick embryos showed that the drug reduced or completely inhibited the production of viral hemagglutinin but failed to modify the rate of multiplication or to reduce the infectivity of the virus. In our experience[23] aureomycin had no effect on the viruses of vaccinia and herpes simplex in either mice or chick embryos.

*Absorption and Excretion in Man.* Studies of the absorption and excretion of aureomycin have been handicapped by the lack of an accurate and uniform method of microbiologic assay of the antibiotic. Since the activity of the drug deteriorates more or less rapidly and irregularly *in vitro*, standard twenty-four-hour dilution series methods such as those used for the determination of penicillin will give variable and erroneous results. The method most widely accepted at present was developed by Dornbush and Pelcak[7] and employs a strain of B. cereus as the test organism, with an incubation period of only four hours at 37°C.

Dowling and his associates[24,25] measured the concentration of aureomycin in the blood, cerebrospinal fluid, urine and milk after giving doses of 0.1 to 1.0 Gm. orally and intramuscularly to adults or equivalent amounts to children. Low peak blood levels were found one hour after intramuscular injection of 0.1 Gm., averaging 0.4 μg. per ml. and rapidly declining over the first six hours. When 0.7 or 1.0 Gm. of the drug was given by mouth the maximal blood levels were reached about six hours later and averaged 1.08 μg. per ml. Aureomycin appeared rapidly in the urine in concentrations up to 128 μg. per ml. from two to four hours after oral administration. Low levels ranging from 0.03 to 0.13 μg. per ml. were found in the cerebrospinal fluid of six among nine patients; these levels corresponded to blood concentrations of 0.13 to 4.0 μg. per ml. In one patient no aureomycin could be detected in the milk when the blood level was 2.0 μg. per ml.

Finland and his colleagues[26,27] found that plasma levels were usually about 2.0 μg. per ml. following oral doses up to 1.0 Gm. every six hours. The maximal rate of excretion in the urine occurred from four to eight hours after ingestion when the concentration ranged as high as 256 μg. per ml. The drug continued to be excreted for two or three days after a single dose of 0.5 or 0.75 Gm. and antibiotic activity equivalent to 12 or 15 per cent of a single oral dose could be recovered by the admittedly crude methods employed. Aureomycin could not be recovered from the bile during oral treatment although bile itself did not inhibit the drug *in vitro*.

Brainerd et al.[28] reported that the maximal serum concentration of aureomycin occurred from two to four hours after an initial dose of 1.0 Gm. by mouth, the levels ranging from 0.3 to 2.5 μg. per ml. Cumulative effects were noted in most individuals who received the drug on a continuous schedule every four to six hours, with levels rising as high as 20 μg. per ml. during a six-hour period. When doses of 0.05 Gm. were given intravenously the serum con-

centration rose sharply to between 0.6 and 5.0 μg. per ml. within five minutes and then declined gradually during the next six hours. However, the intramuscular injection of 0.05 to 0.2 Gm. was rarely followed by measurable concentrations in the blood and a level exceeding 0.15 μg. per ml. was observed only once in twenty-one determinations. These authors were unable to detect aureomycin in the cerebrospinal fluid of two adults who received single oral doses of 1.0 Gm. and in a child following the ingestion of 2.0 Gm. over a period of twenty-four hours.

The results of other studies by Schoenbach,[29] O'Leary,[30] Meads,[31] Harrell[32] and their associates are essentially in agreement with those given previously. It seems clear, therefore, that either the oral or the intravenous administration of aureomycin to human subjects may give blood concentrations within the therapeutic range for many bacteria, as judged by their *in vitro* sensitivities. Intramuscular injection would appear to be less satisfactory since the levels with comparable doses are lower and more erratic. Large amounts of active drug are excreted in the urine whatever the route of administration but relatively little enters the cerebrospinal fluid. However, it should be re-emphasized that current methods for the determination of aureomycin probably permit only a rough approximation in the laboratory of the activity and fate of the drug in the body.

*Dosage and Mode of Administration in Man.* Aureomycin hydrochloride is only moderately soluble and nearly 5 ml. of water or normal saline are required to dissolve 50 mg. of the drug. To inject such a volume of a strongly acid solution intramuscularly causes intense pain. Moreover, intravenous administration is also painful and the subsequent incidence of thrombophlebitis is high. These facts, together with the obvious drawbacks connected with repeated intravenous injections, have led to its use principally by mouth.

A variety of dosage schedules with the oral preparation have been described, the amounts varying from 30 to 100 mg. per kg. and the intervals between doses anywhere from one to six hours. The antibiotic is now put up in 250 mg. capsules and it has been our habit to regard 4 Gm. per day (1 Gm. every six hours) as the "standard" dose for an acutely ill adult of average size. At times when the condition seemed critical we have increased this to 6 Gm. the first day. If the result of treatment is favorable this dose is reduced after two or three days to 2 Gm. or even lower. If nausea is a prominent feature smaller doses at shorter intervals may be given. The taking of milk, aluminum hydroxide gel, phenobarbital, etc., along with the drug has proved helpful. It is very uncommon to be compelled to discontinue treatment altogether on account of nausea.

For intramuscular injection 30 to 50 mg. of the drug in 3 to 5 ml. of fluid together with procaine may be given at six hourly intervals. As has been stated this is a painful proceeding and if buffers are employed to diminish the acidity it must be remembered that the antibiotic rapidly loses its potency in solution at a neutral or alkaline reaction. A new vehicle for its intravenous administration, L (−) leucine, has recently been introduced by the Lederle Laboratories. In 5 ml. of this diluent (containing 131 mg. of leucine) 100 mg. of aureomycin hydrochloride may be dissolved. This can be injected directly at a very slow rate or added to an infusion of isotonic dextrose or saline. As much as 400 or 500 mg. every twelve hours may be given to very seriously ill patients. On the whole, oral administration has obvious advantages.

## CLINICAL USE OF AUREOMYCIN

*Protozoal Diseases.* McVay et al.[33] have recently reported rapid cures in fourteen cases of amebic colitis with aureomycin by mouth. Symptoms rapidly subsided and the stools became negative in a few days. Strains of amebae isolated from three of these were exposed to the drug *in vitro* and it was shown to have an amebacidal effect.

*Diseases Due to Spirochetes.* O'Leary and co-workers[30] reported two cases of acute

syphilis in which the patients were treated orally with aureomycin. Results generally comparable to what would be expected with penicillin were obtained.

*Bacterial Diseases. Coccal Infections:* Finland and his associates[34] treated four patients with pneumococcal pneumonia with aureomycin and reported results entirely similar to those obtained with penicillin. At this clinic we have had the same experience. The authors also described excellent results in one case of meningococcemia. In regard to sixty cases of gonococcal urethritis, however, their findings were different, and they concluded that although the drug was effective it was distinctly inferior to penicillin.[26] It may be remarked, however, that small doses were administered in many of these cases.

Schoenbach[29] and Ross[35] and their colleagues have reported the successful use of aureomycin in localized staphylococcal infections including two cases with positive blood cultures.

*Bacillary Infections.* Among the most brilliant effects of aureomycin are those recorded in the treatment of brucellosis. The first case was reported by Bryer et al.[36] who subsequently added four more cases.[14] The strains involved were Br. abortus and Br. suis. A little later Spink and co-workers[15] treated twenty-four patients with Br. melitensis infection. A recent report of the treatment of melitensis infection was made by Knight et al.[37] who described five additional cases. All of the cases were proven by blood cultures; some were of short duration, some had gone on for many months and some were critically ill. There was general agreement on the results obtained. In every instance the temperature became normal within two to five days after commencement of therapy. Blood cultures almost invariably became sterile quite promptly and the symptoms and signs of disease defervesced with equal speed. It is also to be remarked that relatively small total doses of drug were administered to these patients (1.0 to 2.0 Gm. daily) and that equally good results were recorded with a variety of different treatment schedules. Spink reported an interesting Herxheimer-like reaction at the beginning of treatment in twelve of his twenty-four patients—an abrupt rise in temperature eight to twelve hours after the first dose of aureomycin, accompanied occasionally by symptoms of shock. He recommends a treatment period of eleven days, starting with small doses: 0.1 Gm. in divided doses the first day, 0.6 the second, 1.6 the third and 2.0 each day thereafter. Herrell and Barber[38] have reported excellent therapeutic results in four cases in which patients were treated simultaneously with 3.0 Gm. of aureomycin orally and 2.0 Gm. of dihydrostreptomycin intramuscularly each day for eleven to fifteen days.

Tularemia also responds very favorably to treatment with aureomycin. Woodward et al.[39] recorded its effect in three patients, one of whom was critically ill at the time treatment was begun. In all the response was prompt and striking, being quite as satisfactory as the best results with streptomycin.

In view of its antibacterial powers *in vitro* it is not surprising that aureomycin has been tried in a number of infections due to members of the colon-typhoid group. The first report by Bryer et al.[36] noted its effectiveness in two patients with infection of the urinary tract due to coli-aerogenes. Ten additional cases of urinary tract infection with a variety of organisms including A. aerogenes, E. coli, Proteus and Ps. aeruginosa, several of them mixed with S. viridans and S. fecalis, were reported cured by Rutenberg and Schweinburg.[13] We have had a similar experience at our clinic but on the whole we have been unimpressed by the action of aureomycin in severe infections outside the urinary tract due to Ps. aeruginosa and Friedländer's bacillus in particular.

Disappointing experiences with typhoid fever and Salmonella infections have been reported by Collins et al.[40] We, too, have noted therapeutic failures with bacteria of the Salmonella group. McDermott et al.[41]

concluded that the efficacy of aureomycin in typhoid fever was very much less than that of chloromycetin.

*Pulmonary Tuberculosis.* Steinbach et al.[41a] used aureomycin in the treatment of three young adult patients with extensive acute pulmonary tuberculosis. The drug was administered mostly by mouth in doses of 2.0 Gm. to 4.0 Gm. daily for periods of from thirty-four to ninety-four days. In each case the sputum remained positive for tubercle bacilli and the patient showed no improvement either clinically or by x-ray during the treatment period. All three patients had a prompt therapeutic response to streptomycin after aureomycin was discontinued.

*Diseases Due to Rickettsiae.* Laboratory studies having indicated a powerful antirickettsial action of aureomycin, it followed that some of the first clinical trials of the agent were in this group of diseases. Since chloromycetin had already been proven to be effective in scrub typhus, it was hoped that aureomycin would act similarly. On the whole these expectations have been abundantly justified. Aureomycin has been found to be consistently successful in the treatment of Rocky Mountain spotted fever by Bryer et al.,[36] Cooke,[42] Ross et al.[43] and Harrell et al.;[32] in Q fever by Lennette et al.;[4] in Brill's disease by Schoenbach;[44] in typhus by Knight et al.;[37] and in rickettsialpox by Rose.[45] Its action in all these various types of rickettsial infections has been remarkably uniform. Within twenty-four hours after the first dose there is an obvious change for the better in the patient's clinical condition. He appears brighter, "toxemia" seems less, the temperature is lower and there is welcome relief of headache. At the end of forty-eight hours in most instances the temperature has reached normal levels, where it remains, and convalescence proceeds uneventfully. At times this does not take place until the third day but in any case all observers concede that aureomycin interrupts the course of every rickettsial disease thus far studied in dramatic style. To judge from published reports it appears fully as effective as chloromycetin and is much superior to para-aminobenzoic acid.

*Diseases Due to Filterable Viruses.* Evidence afforded by laboratory experiments warranted an early trial of aureomycin in lymphogranuloma venereum; this was accomplished by Wright et al.[6] In their original paper, amplified by a second,[46] these authors have reported the results of treatment in thirty-five cases. Some of these patients had buboes, some acute proctitis and some rectal strictures. There was a remarkable and surprisingly prompt effect on the buboes. In a very few days they were materially shrunken and follow-up revealed that the remission was sustained. Acute proctitis responded equally well. The proctitis associated with rectal stricture also cleared although the chronic anatomic changes persisted. These authors, from the wealth of their experience in their disease, concluded that aureomycin surpassed any mode of therapy previously used.

All of the aforementioned clinical results with aureomycin might have been anticipated from the laboratory data existing at the time the drug was released for clinical investigation. The most unexpected finding in regard to this antibiotic was its curative effect in "primary atypical" or "virus" pneumonia, which was first reported by Kneeland et al.[47] and confirmed by Schoenbach and Bryer,[48] Finland et al.,[49] and Meiklejohn and Schragg.[50] The findings of all these groups have been essentially identical. Cases conforming to the accepted clinical pattern of atypical pneumonia, many of them with serologic confirmation of the diagnosis and most of them having been demonstrated to be unresponsive to penicillin, have almost without exception responded to aureomycin. In general the type of response resembles that seen in rickettsial diseases, particularly Q fever. That is to say, within eighteen to twenty-four hours there is a definite improvement in the patients' general clinical condition, with lessening of fever, cough, headache and "toxemia." Ordinarily the temperature reaches normal levels at the end of forty-

eight hours and convalescence proceeds smoothly. In our experience, if the treatment is stopped at this juncture a relapse will occur but this may again be brought under control by re-administration of the drug. Perhaps the most interesting aspect of these results is the implication that the agent causing primary atypical pneumonia may belong to the category of larger filterable viruses of the lymphogranuloma-psittacosis group.

*Ocular Conditions.* Braley and Sanders[51,52] described the use of aureomycin mainly as a local application in the form of aureomycin borate, 0.5 per cent solution, in a wide variety of ocular infections. Excellent results were described in conjunctivitis due to staphylococcus, pneumococcus, H. influenzae and Morax-Axenfeld bacillus. Reports of several virus diseases of the conjunctiva and cornea were also included. The drug appeared effective in inclusion conjunctivitis and in one case of trachoma. It was also favorably reported in herpetic conjunctivitis although how this diagnosis was established is not stated. Only eight of twenty-seven patients with epidemic keratoconjunctivitis appeared to benefit from the treatment but the authors state that, even so, aureomycin was more effective than any other agent thus far studied.

*Miscellaneous Conditions.* Seven patients with granuloma inguinale have been treated orally with aureomycin and all of them showed a very satisfactory response according to Wright et al.[46] and Greenblatt et al.[53]

In our own experience as well as in the hands of others aureomycin has had equivocal or negative effects in infective hepatitis and infectious mononucleosis. Although the evidence was not absolutely clear-cut we concluded that it was not effective in the common cold.[54] It has been tried in a number of conditions of undetermined etiology such as rheumatoid arthritis, Hodgkin's disease, periarteritis nodosa, lupus erythematosus disseminatus, ulcerative colitis and Guillain-Barré syndrome without beneficial results. Its action in herpes zoster appears to be equivocal. In our experience herpes simplex is unaffected.

## SUMMARY AND CONCLUSIONS

A general review of the literature on aureomycin, both biological and clinical, indicates that it is an important landmark in the field of antibiotics. Its extremely low toxicity, wide range of activity and absorbability from the gastrointestinal tract combine to make it a powerful therapeutic weapon. To an extraordinary degree it approximates in a single agent the aggregate effects of the sulfonamides, penicillin and streptomycin in addition to its antirickettsial and antiviral properties. Although the factor of expense still influences its widespread use it appears now to be the unquestioned agent of choice in brucellosis, lymphogranuloma venereum, primary atypical pneumonia and possibly granuloma inguinale. In addition it seems to have achieved a place in the treatment of ocular infections. In typhoid fever it would appear to be clearly inferior to chloromycetin. In other fields where chemotherapy and antibiotics have proved useful its versatility places it in the front rank.

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# Clinico-pathologic Conference

## Pneumonia, Skin Eruption, Thrombophlebitis and Azotemia*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. R., (History No. 166026), was a retired postal clerk, seventy-seven years of age, who entered the Barnes Hospital on November 27, 1948, because of a skin eruption associated with cough and fever. The patient was unable to give an accurate history and the information which was available was obtained from his daughter and from correspondence with the physician who had cared for him at home. The family history indicated that one brother had died of "heart trouble" and another of tuberculosis. The patient had no significant exposure, however, to the latter. One sister died of carcinoma. The patient's general health was good until he reached the age of forty-four when he experienced nervousness and loss of weight for which a thyroidectomy was performed. Similar symptoms returned three years later and a second thyroidectomy was done. The patient's symptoms were relieved and he then remained well until one and one-half years before entry when he developed pneumonia. He was treated with a sulfonamide and later with penicillin. During convalescence a red swollen area appeared on the right arm just above the elbow and gradually extended downward over the forearm. At the same time he developed pain in both calves and a red, swollen, cord-like band appeared over the right calf. Similar areas were noted over other parts of his body including the face and the left thumb; gradually all the lesions cleared completely. Studies in a hospital in the patient's own community were said to have been negative; the nature of these procedures, however, was not known.

One month prior to entry the patient developed a severe upper respiratory infection with fever and malaise. He was treated symptomatically without relief and then sulfamerazine therapy orally was instituted. The patient was also given 1 cc. of a repository penicillin preparation three times during a six-day period. Although his general condition improved somewhat, red tender nodules appeared first on his right ankle and right tibia and later over the arms, forearms, left leg and foot. The nodules were said to have been strikingly similar to those which he had developed with his previous infection one and one-half years before. He had low-grade fever with occasional spikes and a persistent hacking cough. Moderate periorbital edema developed and then subsided. A blood count at that time was said to have shown "a marked hypochromic anemia and a moderate leukocytosis." Because the patient failed to improve, three weeks before coming to the Barnes Hospital he entered the hospital in his own community. Reports from that institution stated that his red cell count was 3,100,000 and the hemoglobin 68 per cent. The white blood cell and differential counts were normal. The skin nodules faded but spiking temperatures persisted. At the end of the second week in the hospital the pa-

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tient began to have severe chills and his temperature reached elevations of 103°F. Thrombophlebitis involving the superficial veins in both forearms and in one leg was noted. The patient's condition became worse and following one particularly severe chill his temperature reached 105°F. He developed an urticarial eruption. Following a transfusion of 400 cc. of whole blood he was sent to the Barnes Hospital for further studies.

Physical examination on entry revealed a temperature of 39.2°C., pulse 136, respirations 24 and blood pressure 135/65. The patient was a well developed but poorly nourished, lethargic, obtunded man who was acutely ill. Over the entire skin surface there were many red, raised lesions varying from 2 to 10 cm. in diameter; these were nodular and in some areas circinate with a raised border tending to clear from the center. In addition a number of small urticarial wheals were seen. The skin was hot and dry. Questionable swelling and pain on motion of some of the joints were noted. Many discrete, firm, non-tender, freely movable lymph nodes were palpable in the cervical, axillary and inguinal regions. The eyelids were reddened and rather swollen. The fundi revealed narrowing and tortuosity of the arterioles. No hemorrhages or exudates were seen. Hearing was obviously impaired. The nasal mucosa was red and partial bilateral obstruction was described. The pharynx was injected. The thyroid was not palpable. Signs of emphysema were present and there was slight dullness to percussion at the right base. Decreased breath sounds were noted at both bases posteriorly and in these areas moist sticky rales were heard. The heart was not enlarged. The rate was rapid but the sounds were of good quality. A grade 1 to 2 apical systolic blow was heard. The peripheral arteries were tortuous; those of the feet pulsated. Examination of the abdomen was entirely negative. The prostate was slightly enlarged. Two plus pitting edema of the ankles was present and there was slight swelling of the proximal pharyngeal joints and of the wrists, and some discomfort on flexion of the knees. Neurologic examination was essentially normal.

Laboratory findings were as follows: Blood count: red cells, 2,850,000; hemoglobin, 9 Gm.; white cells, 7,300; differential count: eosinophiles, 1 per cent; stab forms, 4 per cent; segmental forms, 78 per cent; lymphocytes, 14 per cent and monocytes, 3 per cent; platelet count, normal. Urinalysis: albumin, 1 plus; sugar, negative; sediment, showers of granular casts and occasional red cells. Stool examination: guaiac, negative. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 42 mg. per cent; total proteins, 6.8 Gm. per cent; albumin, 3.2 Gm. per cent; globulin, 3.6 Gm. per cent; cephalin-cholesterol flocculation test, 2+; thymol turbidity test, 13.8 units; total bilirubin, 0.86 mg. per cent; prothrombin time, 62.5 per cent of normal; sulfonamide level, 0. Blood cultures: no growth. Sedimentation rate: 1.3 mm. per minute (corrected). Sputum smear: no acid fast organisms seen. Sputum culture: coliform bacilli. Agglutination tests: typhoid, paratyphoid, OX-19 and brucella, all negative. Venous pressure: 80 mm. of sodium chloride. Circulation time (decholin): 12 seconds. Electrocardiogram: occasional auricular premature contraction. Roentgenograms of the chest: "There is peribronchial infiltration in the posterior portions of both lower lobes with no definite evidence of pneumonia."

Shortly after his entrance into the hospital the patient was seen in consultation by a dermatologist who made a diagnosis of erythema multiforme and urticaria. The patient was placed on a regimen which included 100,000 units of penicillin every three hours, a soft diet and supplementary vitamins. He also was given a blood transfusion after which his red cell count rose to 3,070,000 and the hemoglobin to 10.8 Gm. The patient continued to cough up a moderate amount of mucopurulent sputum and rales continued to be audible at both bases.

During his second hospital week he re-

mained rather obtunded. Because of the persistence of rales in the chest another x-ray was taken. This film revealed a great increase in the lung markings bilaterally. A third film taken several days later showed a minimum pleural effusion on the left. Intravenous pyelograms were essentially negative. Gastrointestinal roentgenograms were indeterminate. When the pleural effusion was demonstrated by x-ray examination a thoracentesis was done and 20 cc. of cloudy, light yellow fluid were removed. The fluid had a specific gravity of 1.018 and contained 3.6 Gm. per cent of protein. The fluid contained 2,700 cells with acid of which 76 per cent were polymorphonuclear forms. Culture of the fluid was negative. Repeated urinalyses revealed albuminuria and the sediment showed casts and occasional red cells.

During the first ten days of hospitalization the patient's temperature spiked each day to a maximum of 39.6°C.; on a single day two spikes were recorded. The pulse remained quite elevated. About the eleventh day this patient's temperature receded somewhat but for the following eight days was still slightly elevated. Basal rales persisted and on the eighteenth hospital day the patient coughed up blood-tinged sputum. Bleeding and clotting times were normal but the prothrombin time was 30 per cent of normal. Thrombophlebitis of the veins of the arms and legs became evident and edema of the lower extremities increased markedly. The patient was given amigen daily and more blood transfusions. The skin lesions of erythema multiforme and urticaria varied in intensity but after the administration of amigen became more prominent.

Skin and muscle biopsies were taken and microscopic examination of the sections revealed areas of acute and chronic inflammation of the muscle. The inflammatory cells consisted of polymorphonuclear leukocytes, mononuclear cells and a fair number of eosinophiles. There were no necrotizing lesions of the arterial walls. The dermis revealed very prominent acute and chronic inflammatory changes and large masses of inflammatory cells. A diagnosis of acute and chronic inflammation of the skin and muscles, etiology undetermined, was made.

On the twentieth hospital day the patient again began to have spiking fever which reached 40°C. and continued for four days. Streptomycin therapy was then instituted. During this period of high fever sputum cultures revealed Neisseria and non-hemolytic streptococci. Smears of the sputum, however, also showed gram-negative rods. Physical examination revealed persistent rales at both lung bases.

The patient developed purpuric spots about the eyes and over the arms and trunk. Blood studies by the Hematology Department revealed the following: red cells, 2,970,000; hemoglobin, 10.2 Gm.; white cells, 13,050; platelets, 100,000; reticulocytes, 2.4 per cent; differential count: basophiles, 2 per cent; stab forms, 20 per cent; segmented forms, 73 per cent; lymphocytes, 4 per cent (three of which appeared young) and 1 monocyte. Toxic granules were seen in the polymorphonuclear leukocytes. Coagulation time, 4½ minutes; prothrombin time, 20 seconds; (normal control, 20 seconds); bleeding time, 22 minutes; clot retraction, poor. A diagnosis of thrombocytopenic purpura, probably secondary, was made. Several days later a repeat platelet count was 36,000. The patient exhibited increased difficulty in breathing and oxygen therapy became necessary. Gradually he became weaker although once again he was afebrile. During the last two weeks of life the urinary output on several days was markedly reduced and albuminuria at times was extremely pronounced. Near the end of his hospital course the total proteins were 5.5 Gm. per cent with albumin, 2.1 Gm. per cent and globulin, 3.4 Gm. per cent. The cephalin-cholesterol flocculation test remained at 4 plus and the thymol turbidity was 18.5 units. The non-protein was 38 mg. per cent and the white count had risen to 17,800. On December 25, 1948, the patient's temperature again spiked to 40°C. and he expired.

CLINICAL DISCUSSION

DR. W. BARRY WOOD, JR.: We all will agree that this patient presented an extremely complicated diagnostic problem. From the data available a number of organs which probably were involved by this disease process can be listed: first of all, the skin as indicated by erythema multiforme and urticaria; second, the blood vessels, particularly the veins, as evidenced by the fact that the patient had multiple thrombophlebitis; third, the patient had pain on motion in some of the joints; fourth, moderate lymphadenopathy was recorded. The lungs were the site of abnormal changes and the pleura may also have been primarily affected. The results of the surgical biopsy suggest that the muscle was pathologically involved and finally the anemia and thrombocytopenia suggest changes in the bone marrow involvement. One cannot be certain, however, that the changes in the blood were not secondary rather than primary. Dr. Moore, would you comment on the evidence which suggests that the liver also may have been incriminated?

DR. CARL V. MOORE: The liver function tests were certainly abnormal. Several tests were done and since all the results showed definite deviation from the normal I think one can be quite certain that the liver, like many other organs, was involved.

DR. WOOD: In the face of infection with high fever, such as was present in this case, can one rely on liver function tests to determine whether there is really organic disease damage in the liver itself?

DR. MOORE: I do not believe that an abnormal cephalin-cholesterol flocculation test *per se* would enable one to state that a patient had primary liver disease, but I doubt that the prothrombin time would be altered to the degree that it was here unless there was intrinsic hepatic disease.

DR. WOOD: Would you agree with that, Dr. Shank?

DR. ROBERT E. SHANK: Yes, I would. I believe that the liver can definitely be incriminated.

DR. WOOD: I should like to ask the students to suggest diagnoses which might explain all of the clinical manifestations exhibited by this patient.

STUDENT: Leukemia or lymphoma must be considered.

STUDENT: Polyarteritis nodosa may give rise to this type of clinical picture.

STUDENT: Stevens-Johnson's disease, so-called erythema multiforme exudativum, is characterized by certain features which were recorded here.

STUDENT: Disseminated lupus erythematosus.

DR. WOOD: That diagnosis is less likely here, of course, than it would be had this patient been a woman.

STUDENT: Dermatomyositis.

DR. WOOD: Does anyone care to suggest scleroderma? Certainly all of the collagen diseases must be discussed. Are there any other suggestions?

STUDENT: Buerger's disease should be mentioned in view of the venous involvement but I doubt that it could have caused the entire clinical picture.

DR. WOOD: We now have a considerable number of diagnostic possibilities and we shall attempt to evaluate them in the light of this patient's history and course in order to reach the correct diagnosis. Dr. Taussig, would you comment on the likelihood of leukemia having been the primary disease?

DR. BARRETT L. TAUSSIG: Considering the organs involved in this case, one by one, leukemia may indeed affect the skin and erythema nodosa may occur. Urticaria is certainly not common, however. Thrombophlebitis may be an accompanying complication of any disease process although I do not believe it is particularly common in leukemia. Similarly, the joints are not usually involved unless there is hemorrhage into a joint space. Lymph node enlargement, of course, is common although I would have expected perhaps even more adenopathy than was present in this instance. Although leukemic infiltration in the lungs is reported, I do not think the sequence of events here was particularly

characteristic; pleural involvement is not common. The kidneys and the muscle may be infiltrated with leukemic cells but again I think the changes seen here were rather marked for the usual findings in leukemia. Bone marrow changes, insofar as the red blood cells and the platelets are concerned, are entirely consistent. Considering the situation as a whole, I believe that the findings are not too much in favor of leukemia.

DR. WOOD: Dr. Sale, do you think lymphoma should be considered?

DR. LLEWELLYN SALE, JR.: Although many of the organs which were apparently involved in this instance may be affected in lymphoma, I believe that it is no more likely than is leukemia.

DR. WOOD: Let us inquire whether the hematologists will defend either of these diagnoses.

DR. MOORE: In view of the fact that the skin and muscle biopsy showed chronic inflammatory changes with infiltration of polymorphonuclear leukocytes, I think lymphoma can be ruled out; in lymphoma such infiltration is due to lymphocytic cells.

DR. WOOD: Dr. Goldman, do you think that the clinical picture is compatible with Boeck's sarcoid?

DR. ALFRED GOLDMAN: Neither the skin lesions nor the muscle biopsy findings are characteristic. The pulmonary manifestations, likewise, are not those usually seen in sarcoid although sarcoid may exhibit bizarre patterns in the lungs. Usually, however, the hilar lymph nodes are prominent; and if the process is widespread, miliary infiltration in both lungs is seen. I believe I would reject the diagnosis of sarcoidosis.

DR. WOOD: What is your feeling in regard to Stevens-Johnson's disease, Dr. Scott?

DR. VIRGIL C. SCOTT: Stevens-Johnson's disease, the etiology of which is not known, is manifested chiefly by fever, the lesions of erythema multiforme, particularly of the upper extremities, often with involvement of the pleural cavity and of the genitalia and with skin lesions which are frequently vesicular and bullous. These bullae may rupture and may become secondarily infected. I do not think that this man had Stevens-Johnson's disease.

DR. WOOD: The skin manifestations might be explained on that basis and it is true that pneumonia may occur as a complication. In that regard there is an interesting report from Dr. Finland's laboratory in Boston reporting fatal cases of pneumonia in association with this syndrome.* However, I agree that that diagnosis does not explain all of the findings here and I believe that we can therefore eliminate it from further differential diagnosis. Dr. Smith, what about Buerger's disease?

DR. JOHN R. SMITH: It is quite unlikely that Buerger's disease could have been responsible for all of this man's difficulties. Thromboangitis obliterans when extensive may involve the vessels of all the extremities; it may affect the coronary arteries, cerebral arteries and indeed arteries to any organ. Usually, however, the site of the pathologic process is in the vessels of the legs, parallel involvement of both veins and arteries being common. I doubt that it needs serious consideration in this instance.

DR. WOOD: I would agree that it would be difficult to attribute all of the manifestations in this case to Buerger's disease. We are then left with diseases that are often classified together as diseases of the connective tissue or so-called collagen disease. The latter term is now widely used in the current literature and I think it would be well to discuss these possibilities in detail. Dr. Hampton, do you believe that the findings here are compatible with the diagnosis of polyarteritis nodosa?

DR. STANLEY F. HAMPTON: I think that that diagnosis seems most likely when one reads the protocol; I believe that it would explain the entire clinical picture.

DR. WOOD: In other words, the first diagnosis which would come to your mind,

* FINLAND, M., JOLLIFFE, L. S. and PARKER, F., JR. Pneumonia and erythema multiforme exudativum. *Am. J. Med.*, 4: 473, 1948.

having considered this protocol, would be polyarteritis nodosa. That impression is afforded support by the fact that when this patient had pneumonia, approximately one and one-half years before his final illness, he was given a sulfonamide and after recovery was fairly well until one month before admission when he acquired another respiratory infection and again was given a sulfonamide. Polyarteritis due to sulfonamide hypertensitivity is, of course, a now well known entity and one must therefore consider it seriously in this situation. Dr. Bukantz, do you agree that this patient definitely had polyarteritis nodosa?

DR. SAMUEL C. BUKANTZ: I have some doubt. I agree that most of the findings are extremely typical of polyarteritis with the possible exception of liver involvement. Some changes in liver function may be associated with polyarteritis but I am not aware of them.

DR. WOOD: Polyarteritis may, of course, involve vessels anywhere in the body and thus any organ. I believe the liver may be involved in a significant number of cases and therefore think that the hepatic abnormalities here do not necessarily exclude the diagnosis. What is your view on that subject, Dr. Hampton?

DR. HAMPTON: I agree with you.

DR. WOOD: What about venous involvement in periarteritis?

DR. KEITH S. WILSON: The veins may be involved in the disease. The bone marrow findings disturb me somewhat; I am not sure that they can be explained on the basis of polyarteritis. Perhaps the same drug sensitivity which gave rise to that entity, however, also exerted a toxic effect on the marrow.

DR. WOOD: Let us ask Dr. Moore whether he believes the bone marrow is involved primarily or secondarily here.

DR. MOORE: I do not know. There was no bone marrow aspiration performed on this patient, but I think that there is a definite possibility that the bone marrow involvement was primary for I have seen one other case in which thrombocytopenia occurred in proven polyarteritis nodosa. The bone marrow changes may have been a manifestation of hypersplenism; that is, the spleen may have been involved primarily by polyarteritis and secondarily affected the bone marrow. I do not believe here that these two possibilities can be differentiated. Probably, even if a bone marrow aspiration had been done, the answer to that question could not be determined.

DR. WOOD: I am quite certain that the bone marrow was involved here. I do not think, however, that the clinical manifestations of bone marrow involvement are very common.

DR. WILSON: I think it is much more likely for drug sensitivity *per se* to produce bone marrow changes such as occurred here than for polyarteritis to do so. In addition, I believe that carcinoma of the pancreas should be considered.

DR. WOOD: Multiple venous thromboses occur not uncommonly in carcinoma of the body or tail of the pancreas and therefore that diagnosis should be mentioned. Multiple venous thromboses may occur with other carcinomas, too, may they not, Dr. Scheff?

DR. HAROLD SCHEFF: They may be seen with carcinoma anywhere in the body but are most often associated with carcinoma of the body or the tail of the pancreas.

DR. WOOD: Would you like to suggest, Dr. Wilson, that the entire clinical picture may be explained on the basis of carcinoma of the pancreas?

DR. WILSON: No, I think that the patient had polyarteritis also. However, urticaria and erythema multiforme may be seen as a concomitant of metastatic tumor from any primary source; it is particularly apt to occur if the liver is involved.

DR. WOOD: In other words, skin rashes may develop when the liver is involved by carcinoma.

DR. WILSON: Yes. It would be difficult, however, on the basis of pancreatic carcinoma to explain involvement of the kidney and of the muscles and therefore carcinoma of the pancreas is my second

choice; I do believe that it should be mentioned. As I have said before, I believe that the patient definitely had polyarteritis.

DR. WOOD: It appears that all the members of the allergy division made a single diagnosis; namely, that of polyarteritis nodosa.

DR. GOLDMAN: Does the absence of hypertension disturb any of the allergists in making that diagnosis?

DR. WILSON: There are a number of recorded cases of polyarteritis without renal involvement and those cases do not exhibit hypertension. It is true that approximately 75 per cent of the patients whose kidneys are the site of polyarteritis do develop hypertension.

DR. WOOD: Dr. Goldman, do you have any further comment?

DR. GOLDMAN: Recently Dr. George Baehr was here and discussed the collagen diseases. He made the statement that in the absence of hypertension one of the other collagen diseases should receive primary consideration.

DR. WOOD: Would you want to throw out the diagnosis of polyarteritis on the basis of Dr. Baehr's statement?

DR. GOLDMAN: Not entirely, but I would like to consider other collagen diseases.

DR. BUKANTZ: This discussion brings up a very important point. Classical polyarteritis nodosa is generally associated with hypertension and with lesions of the larger sized arteries; not infrequently occlusion occurs but such cases show no evidence of venous involvement. On this basis some pathologists have raised a question concerning the significance of the experimental form of polyarteritis which has been produced in rabbits, for many of the animals have shown not only arterial lesions but venous lesions as well. The type of diffuse vascular involvement, however, which is associated with hypersensitivity, such as to sulfonamide drugs, is characterized by widespread involvement of the smaller blood vessels. It is this type of vasculitis which resembles the experimental disease produced in rabbits by massive injections of protein. This latter entity is often called polyarteritis nodosa although, as pointed out, it differs from the classical form.

DR. ROBERT J. GLASER: In view of this discussion of venous involvement, I believe a syndrome which is called migratory thrombophlebitis might be discussed. This clinical entity, which is not the one associated with carcinoma of the pancreas or of other organs but rather is associated with rheumatic fever, fits the clinical picture described here quite well. I have seen migratory thrombophlebitis only once and then in a rather young patient who had definite acute rheumatic fever. It has, however, been described by a number of writers and presumably is due to hypersensitivity. As has been noted, this patient also had erythema nodosa which, likewise, is assumed to be a manifestation of hypersensitivity. It seems to me, as Dr. Bukantz has clearly stated, that there is a whole group of diseases characterized by hypersensitivity, particularly to the sulfonamides which are not, at least by pathologists, called polyarteritis. Rather they are simply classified as having been due to sulfonamide hypersensitivity; they may be characterized by vascular involvement of almost any organ.

DR. WOOD: I think the terminology is not as important as an understanding of the general pathogenesis of this group of diseases; actually the term "collagen disease" which is now being used with increasing frequency includes all of these disease entities in one group and yet avoids the argument which Dr. Bukantz and Dr. Glaser have just raised, stressing the minor differences among them. In passing, I should like to ask if anyone would like to support the diagnoses of either lupus erythematosus dissemenata or dermatomyositis.

STUDENT: Dr. Wood, in view of the fact that the biopsy of the skin and muscles did not show necrosis of the arterial walls but definite infiltration of the skin and muscles, would not one be more justified in making a diagnosis of dermatomyositis?

DR. WOOD: I believe that changes noted in the skin biopsy could go along with any of the diagnoses. Their differentiation is a matter of degree and may be most difficult. In summary, I believe it is fair to say that of all the suggestions made by the students, the staff is most enthusiastic about the group of collagen diseases. We have had some difficulty in defining which of the collagen diseases best fits this picture but we lean toward polyarteritis as being most likely. In view of the muscle involvement we realize that the pathologists may make a diagnosis of dermatomyositis; and if such is the case, the clinicians will not be disappointed.

DR. JOSEPH C. EDWARDS: Those of us who observed this patient during his lifetime believed that this was some form of collagen disease although we were not able to distinguish the exact form. The physician who referred the patient to this hospital suggested the possibility of sulfonamide hypersensitivity and also raised the question as to whether penicillin could have been responsible for this entity.

DR. WOOD: I do not recall any of the reports from the literature of proven polyarteritis nodosa following penicillin. Skin sensitivity to penicillin, of course, is well known but I do not believe that full blown polyarteritis has yet been described.

*Clinical Diagnoses:* Diffuse collagen disease, probably polyarteritis nodosa; ? carcinoma of the pancreas.

### PATHOLOGIC DISCUSSION

DR. ANCEL EARP: There was pitting edema of the subcutaneous tissue of the feet and over the skin of the entire body there were numerous irregular purple or blue-black, non-elevated discolorations 0.5 to 5 cm. in diameter. The lungs were attached to the parietal pleura and diaphragm by loose fibrous adhesions and similar adhesions obliterated the interlobar fissures. The right pleural cavity contained approximately 100 cc. and the left 200 cc. of cloudy yellow fluid. The lungs together weighed 3,550 Gm. and were of a uniform fleshy appearance and firm consistency. The cut surfaces bulged slightly and were gray and mottled with irregular red areas. The tissue was smooth and slightly translucent. A moderate amount of brownish red fluid oozed from the cut surfaces; the bronchi contained similar fluid. No gross abnormalities of the pulmonary vessels were noted.

The heart weighed 400 Gm. and in the epicardium there were many punctate ecchymoses. The abdominal cavity contained no free fluid. The right kidney weighed 205 Gm. and the left 180 Gm. The organs were pale and softer than normal. The capsules stripped with ease and finely granular surfaces with occasional flat-based irregular scars ½ to 1 cm. in diameter were exposed. The cut surfaces of the cortex were pale and bulged slightly but the normal markings were easily discernible. Numerous punctate ecchymoses were present in the mucosa of the pelves and ureters. The spleen was moderately hyperplastic. The liver and biliary tract were of grossly normal appearance. Examination of the gastrointestinal tract revealed only focal areas of congestion in the mucosa. The wall of the urinary bladder was moderately trabeculated and the prostate was slightly enlarged.

DR. ROBERT A. MOORE: The dominant gross finding was a peculiar type of pneumonia which involved all lobes in a uniform rather than nodular manner and resulted in a fleshy, reddish gray appearance. It was associated with finely organized adhesions over the pleural surfaces and with pleurisy in the spaces between the adhesions. Except for the enlarged, soft kidneys, the other organs were not grossly remarkable and abnormal change consisted essentially of the presence of petechiae and ecchymoses. Our attention was therefore focused on the problem of the pneumonia.

Microscopically, the picture in the lung varied a good deal from low-power field to low-power field although the sections from all lobes of the lungs were essentially similar. In the region illustrated in Figure 1 the alveolar walls are thickened and enlarged

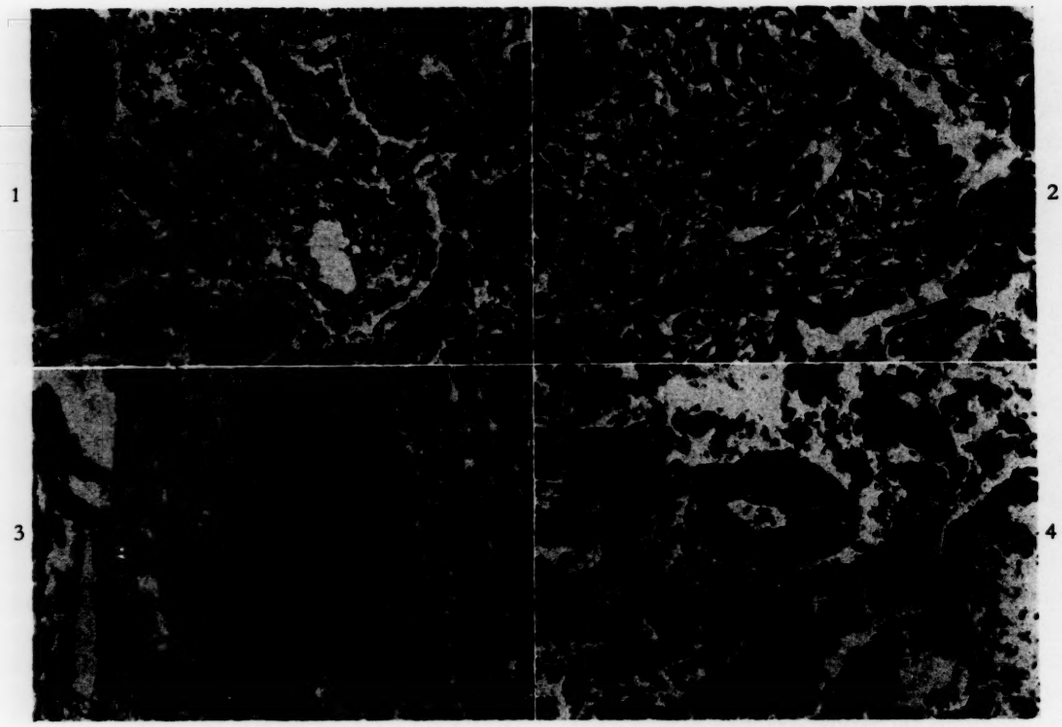


FIG. 1. Pneumonia of an unusual type characterized by a mononuclear infiltration, fibroblastic proliferation in the alveolar walls, metaplasia of the alveolar lining and cells, fibrin and precipitated protein in the alveoli.
FIG. 2. A more detailed view of the fibrous thickening and cellular infiltration of the alveolar walls of the lung and of the cuboidal cells lining the alveoli.
FIG. 3. An interlobular septum of the lung in which there is marked edema, fibrin and a mononuclear infiltration.
FIG. 4. Mononuclear infiltrate in the adventitia of a small artery in the lung without changes in the inner layers.

and the vessels are congested. In some alveoli there are large amounts of granular débris, some fibrin, large cells of the mononuclear type and a few polymorphonuclear leukocytes. The definite increase in thickness of the alveolar walls resulted not only from infiltration with fluid but also from the proliferation of fibroblasts and the infiltration of cells, most of which were lymphocytes and mononuclear cells. Some of the mononuclear cells were in the alveolar lumens and appeared as pulmonary phagocytes. In Figure 2 there is a more detailed view of the alveolar walls with an alveolus which was lined by cuboidal cells. The alveolar wall contains a rather robust fibroblastic stroma infiltrated with cells of the mononuclear and lymphocytic series.

Bacteriologic cultures of the lung revealed a few colonies each of staphylococci, diphtheroids and a Klebsiella organism, but none of these organisms was present in sufficient numbers to indicate that it was responsible for such advanced disease. Bacterial stains of sections of the lung confirmed the impression that these organisms were etiologically not significant, for bacteria could not be identified in either the regions where there were polymorphonuclear leukocytes or mononuclear cells, or in the interstitial tissue or alveoli. Because of the interstitial fibrotic reaction which we thought might have been related to the clinical history of two episodes of pneumonia and because of the presence of myocarditis and interstitial nephritis, as will be described, the possibility of rickettsiae as the etiologic agent was considered but special stains for such organisms were negative. This pneumonia, therefore, can-

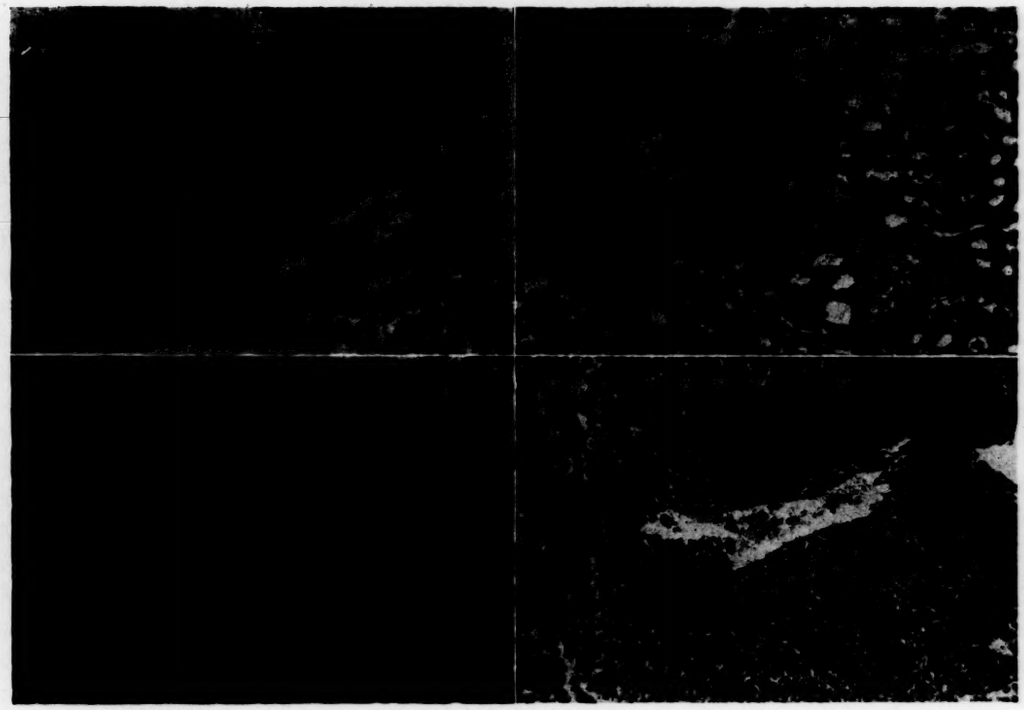


FIG. 5. Sub-intimal mononuclear infiltration of a moderate sized branch of the pulmonary artery without changes in the media or adventitia.
FIG. 6. A focal lesion in the cortex of the kidney about a small necrotic artery which is quite similar to the vascular lesion of disseminated lupus erythematosus.
FIG. 7. Myocarditis composed of an interstitial infiltrate of mononuclear cells.
FIG. 8. Sub-intimal mononuclear infiltration of a vein in the spleen similar to the lesions in larger pulmonary arteries and veins throughout the body.

not be established as having been due to a specific organism.

This peculiar type of pneumonia was characterized by early fibrous organization of interstitial inflammation, co-existent with exudation of leukocytes and mononuclear cells into the alveoli. Further, as illustrated in Figure 3, in the interlobular septa there is tremendous edema and distention of the lymphatic spaces with very slight infiltration of mononuclear cells. Around some of the small blood vessels in the lungs (Fig. 4) there is a definite perivascular cellular infiltrate composed of mononuclear cells with a few lymphocytes. No eosinophilic or neutrophilic leukocytes are present and, so far as we can determine, there is no swelling or fibrinoid change of the collagen. In the intima of some of the blood vessels of the lung, such as the moderate sized branch of the pulmonary artery seen in Figure 5, there is thickening and cellular infiltration of the intima with the same types of cells present in the other infiltrates. In the adventitia and media there are no significant changes.

In the sections of the kidney there were numerous focal lesions in the cortex characterized by separation of the tissue, edema and cellular infiltration with the same types of mononuclear cells, and in the particular instance illustrated (Fig. 6) one of the foci includes a small artery which is definitely necrotic and appears to have been previously swollen by edema and infiltrated by mononuclear cells. In the myocardium (Fig. 7) there are no vascular lesions, but in a few foci increased numbers of mononuclear cells in the interstitial tissue are seen. These cells resemble those of the infiltrates in the other organs and are not the so-called Antischkow myocytes seen in many non-specific inflammations of the myocardium.

An example of a lesion present in many veins is seen in Figure 8 taken from the spleen; throughout the body changes similar to those in the pulmonary arteries are noted in that the endothelium is lifted off the vessel wall and mononuclear cells have infiltrated beneath the endothelium. This lesion is non-specific and is seen throughout the body in a wide variety of diseases.

In sections of the liver there was very definite but slight cirrhosis. There were no vascular lesions in the liver, however, and no cellular infiltration of any significance.

It is our conclusion that the lesion in the lung is to some extent suggestive of the type which occurs in hypersensitivity reactions, but it cannot be explained entirely on that basis. There was something additional in the nature of an interstitial and exudative pneumonia with organization which is not, so far as we are aware, consistent with what has been described and with what we have observed in reactions to the sulfonamide drugs or other sensitizing agents *per se*. On the other hand, the very definite lesions in the kidney cannot be explained on the same basis as the pneumonia. Furthermore, in the biopsy specimen of the muscle there was very definite interstitial myositis with polymorphonuclear leukocytes, and in the myocardium at autopsy there was a focal but definite interstitial myocarditis. The only interpretation of this case that I can offer to fit the clinical and pathologic observations would be as follows:

This patient had pneumonia about one and one-half years before death treated with one of the sulfonamide drugs. Over a year later he again developed pneumonia, the cause of which we cannot demonstrate. He was again treated with sulfonamides and at the time he died was apparently suffering from two diseases, pneumonia of unknown causation and a sensitivity reaction to sulfonamides, manifest in the heart, kidneys and veins throughout the body.

It is a perplexing problem to choose a name for the disease I have described. This patient did not have the lesions of the classical type of polyarteritis nodosa in which there are changes in the adventitia and media of the arteries as well as in the intima, nor were the changes those of dermatomyositis. The artery in the section from the kidney could pass for an artery from a case of disseminated lupus erythematosus, but changes in more than one artery are necessary in order to make that diagnosis. It has, however, become the consensus in the literature in the last few years, and it has certainly been our experience, that these diseases are not the distinct entities pathologically that they were once thought to be; rather they represent expressions of a diffuse disease of collagen which may take different forms in different patients or even in the various organs of a single patient. I believe that this patient did have a sensitivity type of reaction, evidenced by diffuse disease of the collagen, but that in addition he developed pneumonia of some peculiar type which apparently marked the beginning of the terminal episode.

*Final Anatomic Diagnosis:* Atypical pneumonia of all lobes of the lungs; nonsuppurative interstitial nephritis; interstitial myocarditis; sub-intimal mononuclear infiltration in the systemic veins and pulmonary arteries; ecchymoses of the skin, subcutaneous tissues and mucosa of the gastrointestinal tract, renal pelves, urters and epicardium; cirrhosis of the liver, slight.

*Acknowledgment:* Illustrations were made by the Department of Illustration, Washington University School of Medicine.

# Case Reports

## Intestinal Lipodystrophy (Whipple's Disease)*

PAUL J. SCHUTZ, M.D., WILLIAM H. BENNER, M.D. *and* WILLIAM A. CHRISTIAN, M.D.
*Chicago, Illinois*

SINCE 1907 when Whipple first described the entity of intestinal lipodystrophy, twenty-three additional cases presenting similar findings have been reported in the literature. Not all of these can be accepted, either because incomplete histopathologic data have been furnished or because the anatomic findings are somewhat at variance with those Whipple described. Included in the doubtful group are the three early cases described by Pemberton et al.[18] These patients still survive and will probably be reclassified at a later date as acceptable after further observations of their clinical course have been completed. Unfortunately, the diagnosis cannot be made with certainty by clinical study of the living patient because of the nonspecific manifestations of the disease. Only one of Pemberton's patients showed gross involvement of the small bowel and in none of the three was a biopsy of the intestine obtained.

As far as can be determined the case we are reporting is the fifteenth that adequately satisfies the criteria described by Whipple. The diagnosis was made postmortem and was not previously suspected. Our case is noteworthy in the following respects: (1) It closely resembles Whipple's prototype; (2) the patient had been under extended clinical observation at intervals throughout the course of his disease; (3) the laboratory work-up was extensive because of the repeated hospitalizations and uncertainty as to diagnosis.

The syndrome of intestinal lipodystrophy as described by Whipple is "characterized by gradual loss of weight and strength, stools consisting chiefly of neutral fat and fatty acids, indefinite abdominal signs and a peculiar multiple arthritis." All of the acceptable patients to date, except one,[17] have been males in the fourth, fifth or sixth decades of life. The natural history of the disease is usually protracted, with periods of partial remission followed by recrudescence of the relentless downhill course. Terminally the clinical picture is that of extreme malnutrition and cachexia. Another phenomenon sometimes seen is a generalized increase in skin pigmentation[1,3,5,14] which may cause confusion with Addison's disease.[16] The migratory arthralgia[1,3,5,12,13] likewise tends to obscure the true nature of the disease.

Other associated signs and symptoms are anemia, low blood pressure and peripheral pitting edema. These appear late in the disease and are probably secondary manifestations of the poor nutritional status. One patient[11] had hemolytic anemia.

Anatomically the only consistent findings have been "massive accumulations of intracellular and extracellular fat in the small intestine and its draining lymph nodes, with dilatation (probably resultant) of lacteals and mesenteric lymphatics."[17] Three patients[4,5,17] have had chylous ascites but in none has obstruction of the thoracic duct been demonstrated. Fibrous pericarditis, pleuritis and peritonitis have been reported several times but are in no way specific. (Table 1.)

### CASE REPORT

The patient, an American-born white male of Italian parentage, was thirty-five years old

* From the Medical and Pathology Services of the Veterans Administration Hospital, Hines, Ill. Published with permission of the medical director, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

when first admitted on May 24, 1946. He stated that he had been in good health until January, 1944. At that time both ankles became swollen and painful following a long road march (he was in service at the time). He soaked his legs in warm water and by the next morning his symptoms had subsided. The pain and swelling recurred a few days later after another march. He was hospitalized and given a medical discharge because of an old quiescent osteomyelitis of the right fibula, not because of the arthralgia. In March, 1944, he developed "stiffness" of the knees. Since that time he has had similar involvement of his hands, wrists, elbows, shoulders, back and hips at various times. A sojourn in the southwest and repeated trials of physiotherapy were of no benefit. The past history and family history were non-contributory.

Physical examination revealed a well developed, well nourished white male who was not acutely ill. Oral temperature was 98.6°F., respirations 20, pulse 68, blood pressure 114/80, height 67 inches, weight 155 pounds. He walked slowly and carefully, with short steps, but there was no limp. Physical examination was entirely negative except for slight limitation of abduction and elevation in both shoulders, more marked on the left. None of the joints showed signs of inflammation. Laboratory data are summarized in Table II.

X-rays of all joints in both lower extremities failed to reveal arthritic changes. The chest plate was also normal.

At no time during this admission were any manifestations of active arthritis observed. The shoulder disability disappeared and thereafter he was asymptomatic. He was discharged on August 21, 1946.

The significance of the joint pains and their relation to this syndrome is unknown. At this time the patient's nutritional state was good and his bowel function was normal. The laboratory data obtained form a valuable base line with which to compare the observations made after the more classic features of the disease had appeared.

The patient re-entered the hospital on August 11, 1947, complaining of weakness, weight loss, abdominal pain aggravated by deep breathing, decreased sexual potency and increased pigmentation of the skin of three months' duration. He stated that the joint pains and swellings had continued from the time of his last admission until about three months prior to this hospitalization. At that time they disappeared and he first became aware of a peri-umbilical pain which was aggravated by deep breathing. He also developed mild dyspnea on exertion and noticed increasing weakness and fatiguability. The least activity now exhausted him. He had

TABLE I

PREVIOUSLY REPORTED CASES

| Acceptable Cases | | | Doubtful Cases | | |
|---|---|---|---|---|---|
| Author | No. of Cases | Year | Author | No. of Cases | Year |
| Whipple[1] | 1 | 1907 | Blumgart[2] | 3 | 1923 |
| Jarcho[3] | 1 | 1936 | Fleischmann[6] | 1 | 1930 |
| Hill[9] | 1 | 1937 | Collins and Berdez[15] | 1 | 1934 |
| Korsch[8] | 1 | 1938 | Boeck[7] | 1 | 1937 |
| Glynn and Rosenheim[16] | 1 | 1938 | Pearse[10] | 1 | 1942 |
| Reinhart and Wilson[4] | 1 | 1939 | Pemberton et al.[18] | 3 | 1947 |
| Sailer and McGann[5] | 1 | 1942 | | | |
| Apperly and Copley[12] | 1 | 1943 | Total | 10 | |
| Vaux[13] | 1 | 1943 | | | |
| Amsterdam and Grayzel[14] | 1 | 1945 | | | |
| Fitzgerald and Kinney[11] | 1 | 1945 | | | |
| Rosen and Rosen[17] | 1 | 1947 | | | |
| Newman and Pope[19] | 1 | 1948 | | | |
| Chapnick[28] | 1 | 1948 | | | |
| Total | 14 | | | | |

lost about 15 pounds in weight, a circumstance he attributed to his lack of appetite. There had been progressive darkening of the skin of the entire body during this same period.

On physical examination oral temperature was 98.6°F., pulse 78, respirations 18 and blood pressure 105/70. He now weighed 140 pounds. There was a gray-brown pigmentation of the skin, most marked on the hands, face and neck. A few, small, shotty nodes were palpable in the groins. He seemed slightly dehydrated. Laboratory data are summarized in Table III.

TABLE II
COLLECTED LABORATORY DATA, FIRST ADMISSION

| | May, 1946 | | June, 1946 | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 25 | 28 | 13 | 18 | 19 | 22 | 24 | 25 |
| Hemoglobin, Gm. 100 cc. of blood | 14.0 | | | | | | | |
| R.B.C., millions, cu. mm. of blood | 5.1 | | | | | | | |
| W.B.C., thousands, cu. mm. of blood | 9.1 | | | | | | | |
| Sedimentation rate, mm. per hr | ..... | 12 | 19 | 7 | | | | |
| Blood culture | ..... | .. | .. | ..... | Sterile | Sterile | | |
| Routine urine analysis | Negative | | - | | | | | |
| Wassermann test | Negative | | | | | | | |
| Bacterial agglutinations | ..... | .. | .. | Negative | | | | |
| N.P.N., mg., 100 cc. of blood | 34.2 | | | | | | | |
| Urea N, mg., 100 cc. of blood | 14.0 | | | | | | | |
| Uric acid, mg., 100 cc. of blood | 4.1 | | | | | | | |
| Cephalin flocculation test | ..... | .. | .. | Negative | | | | |
| A/G ratio, Gm. per 100 cc./Gm. per 100 cc. | ..... | .. | .. | 3.8/3.7 | | | | |
| Basal metabolic rate | ..... | .. | .. | ..... | ..... | +1 | −4 | +1 |

The electrocardiogram showed right axis deviation, flattening of $T_1$, inversion of $T_2$ and $T_3$ and slight elevation of S-$T_2$ and S-$T_3$. The T wave was flat in $CF_2$ and inverted in $CF_4$. X-rays of the digestive tract revealed no organic or functional disturbance. A chest plate was also negative.

During the first part of his hospital stay he complained bitterly of abdominal pain and distention not relieved by defecation, and of weakness. There was no diarrhea. Irregularly he ran a low grade fever varying from 99.0° to 99.6°F. With symptomatic treatment directed toward improving his nutritional status, his appetite and sense of well being varied from poor to fair. His weight remained fairly constant at about 140 pounds. Despite the absence of positive laboratory findings he was treated for three weeks for Addison's disease. The treatment consisted of a high sodium, low potassium diet, supplemented with 5 mg. of desoxycorticosterone daily. He showed no improvement and this therapy was discontinued.

A low fat, high carbohydrate, high protein diet and fifteen drops of tincture of belladonna four times a day were prescribed. On this management the abdominal symptoms gradually subsided. Early in October he became restless and expressed a wish to return home. He was instructed to continue the dietary and antispasmodic therapy at home and was discharged on October 15, 1947. Despite the symptomatic relief achieved his general physical condition was little better than at the time of admission.

Three years and five months after the onset of the joint pains the patient began to develop signs and symptoms indicative of a systemic wasting disease. Despite clinical evidence of malnutrition the related biochemical findings showed no deficiencies at this time.

No evidence of diminished adrenal or pituitary function could be demonstrated by the laboratory studies. (Table III.) The significance of the elevated basal metabolic rate is obscure. It is without parallel in the literature of Whipple's disease but occurs in about 50 per cent of those with idiopathic steatorrhea.[26,27] There was no evidence of thyrotoxicosis. The thyroid gland was small and symmetrical, there was no tachycardia, tremor or eye signs, the oral glucose tolerance test was normal, there were no

complaints of insomnia, increased nervousness or heat intolerance, and his appetite certainly was not excessive.

The possibility of hemochromatosis was considered but again no substantiating evidence could be found. Hepatic and pancreatic islet function were apparently intact. The exocrine function of the pancreas was not investigated during this admission. Further study was precluded by his insistence on being discharged.

On January 27, 1948, he was admitted for the third time. Following his previous hospitalization he had remained weak and underweight although his family doctor had tried various medications in an effort to build up his health. In November, 1947, he had been given a transfusion of 500 cc. of whole blood daily for seven days. This had produced a marked improvement in his strength and well being which persisted until two weeks prior to this admission.

TABLE III

COLLECTED LABORATORY DATA, SECOND ADMISSION

| | August, 1947 | | | | | September, 1947 | | |
|---|---|---|---|---|---|---|---|---|
| | 12 | 13 | 18 | 26 | 30 | 5 | 10 | 18 |
| Hemoglobin, Gm., 100 cc. of blood | 14.0 | ..... | 12.0 | 14.0 | ..... | ..... | ..... | 12.5 |
| R.B.C., millions, cu. mm. of blood | 5.0 | ..... | 4.35 | 4.6 | ..... | ..... | ..... | 4.34 |
| W.B.C., thousands, cu. mm. of blood | 12.4 | ..... | 12.6 | 12.8 | ..... | ..... | ..... | 14.9 |
| Sedimentation rate, mm. per hr. | ..... | 16 | ..... | 23 | ..... | ..... | ..... | 13.0 |
| Routine urine analysis | Negative | ..... | Negative | | | | | |
| Urine culture | Negative | ..... | ..... | ..... | ..... | ..... | ..... | Negative |
| Urinary urobilinogen, mg. per 100 cc. | ..... | ..... | ..... | ..... | ..... | ..... | ..... | 0.8 |
| Water test (Kepler) | ..... | ..... | Normal | Normal | ..... | ..... | Normal | |
| Urinary chloride, mg. per 100 cc. (Wilder) | ..... | ..... | ..... | ..... | 54.6 | | | |
| Bleeding time, minutes | ..... | ..... | ..... | ..... | ..... | 1.5 | | |
| Coagulation time, minutes | ..... | ..... | ..... | ..... | ..... | 3.0 | | |
| N.P.N., mg., 100 cc. of blood | 31.6 | 34.7 | | | | | | |
| Urea N, mg., 100 cc. of blood | ..... | 13.7 | | | | | | |
| Glucose, mg., 100 cc. of blood | ..... | 82.3 | ..... | ..... | ..... | ..... | ..... | 79.7 |
| $CO_2$ combining power, vol., 100 cc. of plasma | ..... | 44.0 | 52.0 | | | | | |
| Sodium chloride, mg., 100 cc. of blood | 618.0 | 573.0 | ..... | 635.0 | ..... | ..... | 638.0 | |
| Potassium, mg., 100 cc. of serum | 17.0 | 19.2 | ..... | ..... | ..... | 21.6 | | |
| Sodium, mg., 100 cc. of serum | ..... | 307.2 | ..... | ..... | ..... | 328.0 | | |
| A/G ratio, Gm. per 100 cc./Gm. per 100 cc | 4.2/2.8 | | | | | | | |
| Cephalin flocculation test | ..... | ..... | ..... | ..... | ..... | ..... | ..... | Negative |
| Thymol turbidity, units | ..... | ..... | ..... | ..... | ..... | ..... | ..... | 2.0 |
| Bilirubin, mg., 100 cc. of serum | ..... | ..... | ..... | ..... | ..... | ..... | ..... | 0.5 |
| Bromsulfalein test | ..... | ..... | ..... | ..... | ..... | ..... | ..... | No Retention |
| Amylase, units, 100 cc. of serum | ..... | ..... | ..... | ..... | ..... | ..... | ..... | 46.1 |
| Cholesterol, mg., 100 cc. of plasma | ..... | ..... | ..... | ..... | ..... | ..... | ..... | 139.0 |
| Cholesterol esters mg., 100 cc. of plasma | ..... | ..... | ..... | ..... | ..... | ..... | ..... | 93.0 |
| Basal metabolic rate | ..... | + 15 | +21 | +46 | | | | |
| Urinary 17-ketosteroids, mg. per 24 hr | ..... | ..... | ..... | ..... | ..... | ..... | ..... | 16.2 |
| Urinary prolan A (Cutler and Owen) | ..... | ..... | ..... | ..... | ..... | ..... | ..... | Normal |
| Bacterial agglutinations | Negative | | | | | | | |
| Kahn and Wassermann tests | ..... | ..... | ..... | ..... | Negative | | | |
| Oral glucose tolerance test | ..... | ..... | Normal | | | | | |

when he again became weak and dyspneic. He also began to develop a rather marked, painless diarrhea, which was worse at night and which was accompanied by abdominal distention. His return at this time was prompted by a desire for more blood transfusions which he believed were very beneficial.

The patient now appeared chronically ill and was quite emaciated. Oral temperature was 98.6°F., pulse 116, respirations 18, blood pressure 104/68 and weight 120 pounds. There were a few crepitant rales audible at the base of the right lung. The abdomen was slightly protuberant and there was moderate generalized tenderness on deep palpation. The liver and spleen were not palpable. The remainder of the examination was not remarkable. Laboratory data are summarized in Table IV. The chest plate showed normal lung fields and a normal cardiac shadow.

Because of a fair blood count he was not given a transfusion. He was placed on a high carbohydrate, high protein, low fat diet fortified with a multivitamin preparation. From January 27th to February 3rd his temperature rose daily to 100°F. After that date it fell to 98.6°F., with an occasional afternoon rise to 99°F. Because of the asthenia suggestive of Addison's disease the Kepler test[22] was repeated. Again it was normal.

The diarrhea was not severe, consisting of two or three loose stools daily which were usually passed at night. Following administration of paregoric the consistency of the stools increased and their frequency diminished. A brief course of pancreatin therapy failed to affect the diarrhea appreciably.

He again tired of hospital routine and his failure to improve and insisted on going home. He was discharged on February 17, 1948.

By this time all classic features of the disease were or had been present: loss of weight, weakness, abdominal pain and distention, diarrhea, arthralgia and increased pigmentation of the skin. Again no evidence supporting the diagnoses of Addison's disease, hemochromatosis or hyperthyroidism was elicited by the examiners at the time of admission or by the authors after reviewing the records. The outstanding feature at this time was the continued downhill course, with progressive loss of weight and strength.

The patient was admitted on June 19, 1948, and was observed by one of us (P. J. S.) His complaints at this time were progressive weakness and weight loss and failure of his appetite to improve. The diarrhea had recurred almost at once following his discharge in February. He averaged about twelve stools daily, with no associated abdominal distress. For four weeks prior to admission the diarrhea had been continuous. The stools were watery, frothy and very foul-smelling. He frequently noticed undigested food, such as green beans and corn, in the stool. The color of the stool varied from gray to yellow-brown. Since February he had lost 16 pounds in weight and during this time had noticed progressive swelling of his ankles and legs. This edema showed no diurnal variation.

TABLE IV
COLLECTED LABORATORY DATA, THIRD ADMISSION

| | January, 1948 | February, 1948 | |
|---|---|---|---|
| | 28 | 2 | 12 |
| Hemoglobin, Gm., 100 cc. of blood | 11.0 | | |
| R.B.C., millions, cu. mm. of blood | 4.56 | | |
| W.B.C. thousands, cu. mm. of blood | 11.6 | | |
| Hematocrit | 35.0 | | |
| Routine urine analysis | Negative | | |
| Kahn test | Negative | | |
| N.P.N. mg., 100 cc. of blood | 34.2 | | |
| Glucose, mg., 100 cc. of blood | 80.0 | | |
| Cholesterol, mg., 100 cc. of plasma | ..... | 119.0 | |
| Cholesterol esters, mg., 100 cc. of plasma | ..... | 76.0 | |
| Serum bilirubin, mg., 100cc. of serum | ..... | 0.5 | |
| Phosphorus, mg., 100 cc. of serum | ..... | 4.0 | |
| Alkaline phosphatase (Bodansky units) | ..... | 4.6 | |
| Amylase, units, 100 cc. of serum | ..... | 34.0 | |
| Lipase, cc. of N/20 NaOH per cc. of serum | ..... | 1.1 | |
| Thymol turbidity | ..... | 2.0 | |
| Potassium, mg., 100 cc. of serum | ..... | 20.4 | |
| Urea N, mg., 100 cc. of plasma | ..... | ..... | 12.0 |
| Sodium chloride, mg., 100 cc. of plasma | ..... | ..... | 632.0 |
| Water test | ..... | ..... | Normal |

On physical examination the patient was markedly cachectic. Oral temperature was 98.6°F., pulse 100, respirations 20, blood pres-

TABLE V

COLLECTED LABORATORY DATA, LAST ADMISSION

| | June, 1948 | | | | | | July, 1948 | |
|---|---|---|---|---|---|---|---|---|
| | 20 | 22 | 23 | 25 | 29 | 30 | 7 | 8 |
| Hemoglobin, Gm., 100 cc. of blood | 12.0 | ..... | 12.0 | | | | | |
| R.B.C., millions, cu. mm. of blood | 3.83 | ..... | 4.22 | | | | | |
| W.B.C., thousands, cu. mm. of blood | 7.8 | ..... | 9.1 | | | | | |
| Platelets, thousands, cu. mm. of blood | 229.8 | | | | | | | |
| Clotting time, minutes | 5.0 | | | | | | | |
| Bleeding time, minutes | 2.0 | | | | | | | |
| Prothrombin time, seconds | 14 | | | | | | | |
| Mean corpuscular volume, cu. micra | ..... | 87 | | | | | | |
| Mean corpuscular hemoglobin, micromicrograms | ..... | 26 | | | | | | |
| Color index | ..... | 0.83 | | | | | | |
| Hematocrit | ..... | ..... | 34 | | | | | |
| Routine urine analysis | Negative | | | | | | | |
| Glucose, mg., 100 cc. of blood (fasting) | ..... | ..... | ..... | ..... | ..... | 50 | | |
| N.P.N., mg., 100 cc. of blood | ..... | ..... | ..... | ..... | ..... | 46.8 | | |
| Potassium, mg., 100 cc. of serum | ..... | ..... | ..... | ..... | ..... | ..... | 15.4 | |
| A/G ratio, Gm. per 100 cc./Gm. per 100 cc. | ..... | 1.8/1.7 | ..... | ..... | ..... | 2.4/1.8 | | |
| Cephalin flocculation test | ..... | ..... | Negative | | | | | |
| Thymol turbidity test | ..... | ..... | 0 | ..... | ..... | 1.0 | 1.0 | |
| Butter-choline fat absorption test (Popper et al.) | ..... | ..... | ..... | ..... | Abnormal, very deficient | | | |
| Bilirubin, mg., 100 cc. of serum | 0.15 | | | | | | | |
| Cholesterol, mg., 100 cc. of plasma | 86 | ..... | ..... | ..... | ..... | 72 | | |
| Cholesterol esters, mg., 100 cc. of plasma | 59 | | | | | | | |
| Kahn and Wassermann tests | Negative | | | | | | | |
| Oral glucose tolerance | ..... | ..... | ..... | ..... | ..... | Abnormal low curve | | |
| Calcium, mg., 100 cc. of serum | ..... | ..... | 7.5 | | | | | |
| Phosphorus, mg., 100 cc. of serum | ..... | ..... | 2.8 | ..... | ..... | ..... | 2.3 | |
| Alkaline phosphatase (Bodansky units) | ..... | ..... | ..... | ..... | ..... | ..... | 3.8 | |
| Vitamin A, micrograms, 100 cc. of blood | ..... | 20.0 | | | | | | |
| Carotene, micrograms, 100 cc. of blood | ..... | 0 | | | | | | |
| Weight of "wet" stool, Gm. per 24 hr | ..... | 781.0 | ..... | ..... | ..... | 145.0 | ..... | 211.0 |
| Total stool nitrogen, Gm. per 24 hr | ..... | ..... | ..... | ..... | ..... | 0.99 | | |
| Total stool fat, Gm. per 24 hr | ..... | 20.87 | ..... | ..... | ..... | ..... | ..... | 3.47 |
| Stool fatty acids, Gm. per 24 hr | ..... | 13.81 | ..... | ..... | ..... | ..... | ..... | 2.22 |
| Stool neutral fat, Gm. per 24 hr | ..... | 7.8 | ..... | ..... | ..... | ..... | ..... | 1.25 |
| Stool culture | ..... | ..... | Negative | ..... | ..... | ..... | Negative | |
| Gastric acidity (free and total) | ..... | ..... | ..... | Normal | | | | |

sure 96/64 and weight 102 pounds. The skin showed a dusky, gray-brown pigmentation. The sclerae were not icteric. There was slight atrophy of the mucosa of the free margin of the tongue but no frank glossitis or stomatitis. A small amount of mucopurulent material was adherent to the posterior pharyngeal wall. The chest and abdomen showed extensive wasting of the superficial tissues and musculature. The breath sounds were accentuated and bronchovesicular in character over both lungs. The heart was normal. The abdomen was slightly distended, somewhat tense and there was slight generalized tenderness. The liver, spleen and kidneys were not palpable. The fingers showed early clubbing. The laboratory data are summarized in Table v.

X-rays of the chest were negative. Gastrointestinal films showed hypermotility of the stomach and a small bowel pattern considered characteristic of chronic nutritional deficiency. There was segmentation of the intestinal loops, coarsening of the mucosal pattern and a tendency of the barium to puddle. (Fig. 1.) The gallbladder readily concentrated the radiopaque dye.

At the time of admission the patient was passing about twelve mushy, gray-tan stools daily. They were frothy, foul-smelling, bulky and contained gross particles of undigested food. He was placed on a high carbohydrate (low in polysaccharide content), high protein, low fat diet. Other therapy given included brewers' yeast, multivitamins, parenteral vitamin B complex, vitamin K, crude and refined liver extract, folic acid, pancreatin, and daily blood and plasma transfusions. The number of stools diminished somewhat, as did the total bulk of feces, but the character of the excreta remained unchanged. Because of the low serum vitamin A level 75,000 units of vitamin A were given daily.

His nutritional state continued to deteriorate despite all therapeutic efforts. His daily food intake varied from 300 to 1,900 calories. Intravenous alimentation was difficult because of his tendency to develop pulmonary edema after receiving small quantities of fluids. The pitting edema of the legs resisted all efforts at treatment, including mercurial diuretics.

On July 8th he passed a large amount of dark, red blood via the rectum. He was given 1,000 cc. of whole blood. Two days later he expired suddenly, having remained conscious until an hour before his death.

During the last admission the patient was

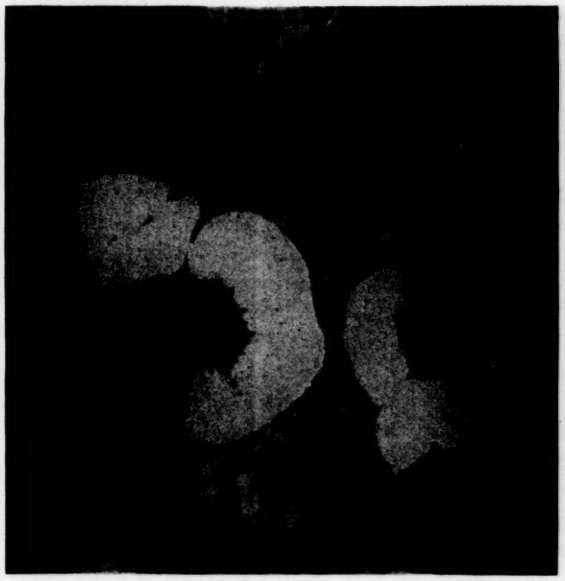

FIG. 1. X-ray of small bowel showing an early stage of disordered motor function due to nutritional deficiency. Note coarsening of mucosal pattern and dilatation of intestinal loops. An early moulage sign is seen.

studied from two standpoints, one diagnostic, and the other nutritional. Although the stools appeared to contain an excessive amount of fat clinically, this was not conclusively established. Fecal fat content, both normal and pathologic, is measured in percentage of the dried twenty-four-hour fecal output.[20] In this case the stools were weighed in the fresh "wet" state, and the fat fractions were extracted without previously dehydrating the specimen. Thus Fowweather's first criterion could not be applied to these data, and it cannot be definitely stated that a relative increase in total fat content of the feces existed. However, the quantities of neutral fat and fatty acid were accurately assayed and on two occasions these values were within normal limits. (Table v.)

Despite the difficulty in evaluating laboratory data the patient was clinically considered to have steatorrhea. Four conditions were considered in the differential diagnosis: biliary tract disease, pancreatic insufficiency, idiopathic steatorrhea and tuberculous mesenteric adenitis.

Normal visualization of the gallbladder, absence of jaundice and presence of urobilinogen in the urine established the normalcy of the biliary tract. Pancreatic steatorrhea was ruled out by the preponderance of hydrolyzed fat in the stool, absence of azotorrhea and lack of response to oral pancreatic extract.

Idiopathic steatorrhea was next considered.

In addition to the wasting, asthenia, diarrhea and skin pigmentation, the following points of similarity were found when our data were compared with the criteria tabulated by Bockus:[27] (1) homogeneous greasy stool; (2) about 35 per cent of fecal fat excreted as neutral fat and 65 per cent as fatty acids and soap; (3) excretion of nitrogen in the stool less than 3.5 Gm. for a twenty-four-hour period; (4) fasting hypoglycemia; (5) a flat, oral glucose tolerance curve; (6) evidence of low blood lipids and low fat tolerance; (7) low blood cholesterol; (8) low serum calcium; (9) elevated basal metabolic rate (on previous admission, not checked before death); (10) anemia and (11) low plasma proteins.

There were, however, some important links missing from the chain of evidence. The most obvious deficiency was the absence of macrocytic hyperchromic anemia. It is known that the anemia associated with idiopathic steatorrhea may vary from simple hypochromic anemia in the early stages and during periods of remission to one indistinguishable from pernicious anemia in the later advanced stages of the disease.[26] Furthermore, it has been shown that when the anemia is in a macrocytic hyperchromic phase parenteral administration of liver extract may be followed by a fall in the color index to a value less than unity. The anemia then responds to iron therapy exactly like any secondary anemia due to iron deficiency.[25] Since our patient was in an advanced stage of the illness, the absence of hyperchromia and macrocytosis was difficult to explain.

The essential normality of the mucous membranes of the mouth and tongue was the second discordant factor. One of the most characteristic features of the sprue syndrome is the appearance of crops of vesicles on the tongue and lining of the cheek, which later rupture and form painful aphthous ulcers. With the exception of minimal atrophy of the papillae along the margin of the tongue, there was no evidence of recent or old stomatitis or glossitis in our patient.

Because of these discrepancies in the clinical picture a clear cut diagnosis of idiopathic steatorrhea could not be made. The possibility of tuberculous mesenteric adenitis was not considered seriously because the patient was not toxic, the lungs were free of disease and the bulk of evidence was in favor of some defect of intestinal absorption.

As a secondary problem the pathophysiologic basis of the patient's poor nutritional state was investigated. Attention was focused on the capacity of the bowel to digest and absorb fat. Recently it has been shown by Popper et al.[24] that when a standard amount of fat and lipotropic substance (e.g., butter and choline) are ingested the subsequent rise of serum thymol turbidity is an accurate index of the intestinal ability to absorb fat. The normal individual will show a rise in thymol turbidity of 200 to 400 per cent over the fasting level. Using this test we found that the thymol turbidity test, both before and after ingestion of the butter-choline mixture, was consistently negative (i.e., there was no detectable turbidity in the solution). This was interpreted as indicating that little if any fat was being absorbed from the bowel. When rechecked the next day the thymol turbidity was 1.0 units, tending to corroborate the low values previously obtained. The deficiency of intestinal fat absorption was also manifested by the low serum calcium and by the low serum vitamin A level which on one occasion was 19.5 micromicrograms (10.9 micromicrograms as ester, 8.6 micromicrograms as the alcohol).

A similar defect in carbohydrate absorption was evidenced by the low flat curve obtained with the oral glucose tolerance test.

It was concluded that the patient was suffering from an obscure metabolic defect, characterized by decreased absorptive efficiency of the intestinal tract, closely resembling idiopathic steatorrhea. Further studies were interrupted by the patient's death.

### AUTOPSY FINDINGS

At autopsy the essential findings were confined to the abdomen. There were 1,500 cc. of straw-colored fluid in the peritoneal cavity. The small intestine was rather opaque and homogeneous grayish yellow in color. There was no suggestion of a lacteal pattern grossly, but the intestinal wall was grossly infiltrated to about three times normal thickness. This thickening was diffuse and uniform and involved all of the small bowel. On opening the bowel there was a moderate amount of dark bloody fluid along its entire course. The mucosal folds were somewhat thickened and prominent but showed symmetrical arrangement. There were scattered petechial hemorrhages in the mucosa, more profuse in the distal two-thirds of the ileum, where they became confluent and gave a diffuse

hemorrhagic appearance to large areas. There were no gross ulcerations anywhere in the gastrointestinal tract. The hemorrhagic character of the intestinal mucosa ended abruptly at the ileocecal valve. The esophagus, stomach and colon were entirely normal.

The most conspicuous abnormality was found in the mesentery of the small bowel. (Fig. 2.) There were numerous pinkish-gray lymph nodes measuring up to 3 cm. in their greatest diameter. They were sometimes separate, more often adherent to several others. These masses of nodes, although apparently confluent, showed no actual fusion as the individual nodes were well demarcated on cut section. The general contour of the nodes was symmetrical, their enlargement being concentric. The cut surface of all the nodes showed a finely honeycombed, spongy appearance. The spaces contained an amber, clear, liquid greasy material which could easily be expressed.

The thickening of the mesentery was found to be due to the extensive adenopathy and not to any intrinsic infiltration. Similar lymph node enlargement was also found at the origin of the coeliac axis artery and among the pre-aortic nodes. The peribronchial, mediastinal and superficial lymph nodes were not involved. The other abdominal and thoracic viscera and the endocrine glands were grossly normal.

Microscopic sections taken from the duodenum, jejunum and ileum showed uniform involvement which was characterized by a heavy infiltration of the mucosa with foam cells. These mononuclear macrophages were arranged in dense sheets, filling in particular the villi, which were thick, club-like and top heavy. (Fig. 3.)

The stroma of the mucosa contained numerous, large, empty vacuoles measuring from fifty to several hundred micra in diameter. The cellular infiltration and the vacuolization had greatly distorted the normal mucosal pattern. The submucosa was also thickened and contained many ovoid and elongated channels, some of which were lined by endothelial cells while the walls of others apparently consisted only of a condensation of the connective tissue stroma. Frozen sections stained with Sudan IV revealed that the small droplets in the cytoplasm of the foam cells readily took the fat stain. The large vacuoles in the submucosa everywhere contained a homogeneous material which also stained brilliantly with Sudan IV. (Fig. 4.)

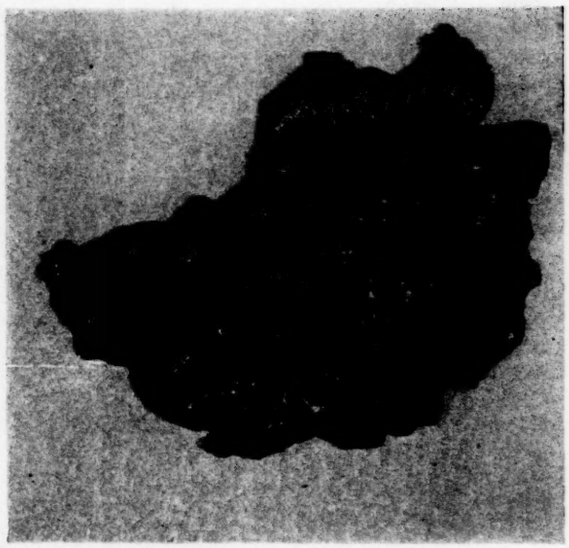

FIG. 2. Mesentery of small bowel demonstrating extensive lymphadenopathy.

The muscular coat of the bowel showed no hypertrophy. The serosa was slightly swollen and contained scattered round cells. Occasionally, dilated lymph channels were seen in the subserosa but they were much less prominent than in the submucosa. Neither inflammatory exudate nor giant cells could be found in the various layers of the bowel wall.

The mesenteric nodes universally presented similar changes. The honeycomb effect produced by the vacuoles was even more prominent microscopically than grossly. Everywhere throughout the nodes were ovoid spaces of varied size. They appeared to be lined with a single layer of endothelial cells. The parenchyma of the nodes was greatly reduced in amount, being compressed into irregular strands and trabeculae between the dilated spaces. The architecture was completely obscured. Rarely, a lymph follicle could be delineated. The irregular columns of parenchymal tissue consisted of a haphazard mixture of reticuloendothelial cells, scattered lymphocytes, islands of foam cells similar to those in the intestinal mucosa, a few neutrophiles and a scanty connective tissue framework. Occasional giant cells were found, sometimes lying in the lumina of the vacuoles but usually in the subjacent stroma forming the wall of the space. (Fig. 5A.) These cells contained from three to ten nuclei which were uniform in size and scattered throughout the cytoplasm. The honeycombing of the parenchyma with lipid-containing vacuoles was uni-

FIG. 3. Intestinal mucosa showing thickening of the villi and compression of stroma by mononuclear foam cells and large vacuoles.

FIG. 4. Small bowel; the distended lymphatics and vacuole-like spaces contain material staining deep orange with Sudan IV.

FIG. 5. A, lymph node; foreign body giant-cell reaction at the margin of a large vacuole. B, the many vacuoles in the nodes, as in the intestinal mucosa, contain material staining an intense orange with Sudan IV.

form in all nodes but the relative frequency of the giant cells varied from node to node.

Frozen sections stained with Sudan IV showed that all the spaces contained a homogeneous substance which stained an intense orange. (Fig. 5B.) The connective tissue capsule of the various nodes showed marked fibrous thickening and contained many dilated lymph channels.

The rest of the gastrointestinal tract, liver, spleen, pancreas, kidneys, adrenals, thyroid, prostate and lungs were microscopically normal. The myocardium showed areas of brown atrophy characterized by collections of golden brown pigment granules at the poles of the nuclei. The staining quality of these granules with Sudan IV was poor and inconsistent.

The pathologic diagnoses were malnutrition, ascites (non-chylous), brown atrophy of the heart and intestinal lipodystrophy.

## CONCLUSIONS

A case of intestinal lipodystrophy is presented. The syndrome should be considered in the differential diagnosis of protracted diarrhea, especially when the patient is a male in middle life. The diagnosis can only be presumptive before death unless adequate surgical biopsies are done at laparotomy.

This case sheds no light on the etiology of intestinal lipodystrophy but demonstrates the importance of poor intestinal absorption in producing the final cachectic phase. Intestinal lipodystrophy may closely simulate clinically most of the features of idiopathic steatorrhea.

*Acknowledgments.* We wish to express our gratitude to Dr. Smith Freeman of Northwestern University and Drs. Frederick Steigmann and Hans Popper of Cook County Hospital and Hektoen Institute for their courtesy in making their laboratory facilities available to us.

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# Thrombocytopenic Purpura Complicating Radioactive Phosphorus Treatment in a Patient with Polycythemia Vera*

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BECAUSE of the rapidly increasing use of radioactive elements in the treatment of disease, possible undesirable effects of these materials are of considerable importance. The present report concerns a patient with polycythemia vera who developed thrombocytopenic purpura associated with striking morphologic changes in the megakaryocytes after treatment with radioactive phosphorus.

It has been clearly established that $P^{32}$ given internally in therapeutic doses is capable of depressing all of the major hemopoietic elements of the marrow with corresponding changes in the peripheral blood. Following a therapeutic dose the white blood cells and platelets may be depressed quite promptly within the first six weeks; the leukopenia is usually maximal somewhat before the thrombocytopenia. Decrease in the red blood cells is more delayed and usually is not noted until the white cells and platelets have begun to return toward normal. The sequence of changes in the blood is presumably related to the normal rate of maturation and length of survival of the different formed elements.

Several reports indicate that in some instances thrombocytopenia may be the most important undesirable effect of radioactive phosphorus therapy. Hall, Watkins, Hargraves and Giffin[1] reported the cases of twelve patients with polycythemia vera treated with $P^{32}$ and noted significant thrombocytopenia in four patients, the lowest platelet counts ranging from 29,000 to 86,000 per cu. mm. The maximal depression of platelet values occurred in one to two months after the medication was given. There was no clinical purpura except for the occurrence of petechiae on the lower extremities in these patients.

Hempelman, Reinhard, Moore, Bierbaum and Moore[2] reported a group of one hundred patients with various hematologic disorders who were treated with radioactive phosphorus. Some of the thrombocytopenia noted may have been a part of the original disease rather than a result of treatment, but the authors believed that the $P^{32}$ contributed to a significant fall in platelets in forty-four patients. Among eighteen patients with polycythemia vera there were two in whom the platelet counts fell to below 100,000 per cu. mm., and one in whom the value was below 50,000 per cu. mm. One fifty-nine year old woman with polycythemia vera was given 7.56 mc. of radioactive phosphorus orally and about one month later developed a platelet count as low as 29,000 per cu. mm. At this time the patient had petechiae on the lower extremities but no other purpuric manifestations. There was spontaneous recovery from this episode of thrombocytopenia.

## CASE REPORT

The patient, E. R., was a sixty-seven year old, white, married woman who was referred to the Simpson Memorial Institute in May, 1947. She

* From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan, Ann Arbor, Mich.

gave a history of loss of strength and decrease in weight which had begun about two years previously. At about the same time she had noticed varicose veins of her lower extremities and these had been treated by injection and ligation. About a year after the onset of these symptoms she became more seriously ill with dizziness, anorexia and shortness of breath on exertion. At that time it was first noted that her eyes were becoming injected and her lips were a dusky purple. Three or four months later, in November, 1946, it was found that her spleen was enlarged and that the blood picture was that of polycythemia. Several phlebotomies were performed. Early in 1947 the patient suddenly lost consciousness while descending her cellar stairs, fell and suffered a laceration of her forehead. Following this accident there was paralysis of the right lower extremity and a diagnosis of cerebrovascular accident was made. There was quite a prompt recovery from the paralysis and the patient was started on a course of x-ray therapy by her local physician, using 200 kv. irradiation with added filtration of 0.5 mm. Cu and 1.0 mm. Al, 50 cm. target skin distance. Between January 8th and January 27, 1947, she received 30r in air to one field per day, to a total of 60r to each of four fields over the anterior and posterior trunk. Between February 18th and February 26, 1947, she was given 200r to each of six small fields over the spine, sternum and extremities.

The irradiation treatment was followed by some improvement in symptoms and partial correction of the blood values but the red blood cell count and hemoglobin remained definitely elevated.

When the patient was examined in May, 1947, she showed evidence of weight loss and there was distinct cyanosis of the skin and mucous membranes. Retinal veins were greatly dilated and of a deep red color. The blood pressure was 156/92. The liver border was felt just below the right costal margin and the spleen extended 3 cm. below the left rib margin on inspiration. There were varicose veins of the lower extremities and stasic dermatitis was present. Chest x-ray was normal except for pleural scarring and calcified nodes. The urine contained a 1+ albumin but was otherwise normal.

TABLE 1

HEMATOLOGIC CHANGES FOLLOWING TREATMENT WITH RADIOACTIVE PHOSPHORUS

| Date | Red Cells (million) | Hemoglobin (Gm.) | Hematocrit (percent) | Platelets | White Cells | Neutrophiles | Lymphocytes | Monocytes | Eosinophiles | Basophiles |
|---|---|---|---|---|---|---|---|---|---|---|
| May 13, 1947.... Phlebotomy | 8.9 | 17.5 | 66 | 115,000 | 14,900 | 69 | 11 | 19 | 1 | 0 |
| May 28, 1947.... $P^{32}$ 8.4 mc. | 7.1 | 16.8 | 62 | 117,000 | 13,300 | 71 | 17 | 11 | 0 | 1 |
| July 9, 1947..... | 6.8 | 15.5 | 54 | Below 5,000 | 7,250 | 70 | 20 | 9 | 1 | 0 |
| July 23, 1947.... | 5.1 | 11.0 | 42 | Below 5,000 | 4,100 | 30 | 47* | 20 | 3 | 0 |
| August 5, 1947... | 4.5 | 11.0 | 36 | 23,000 | 2,450 | 34 | 54 | 12 | 0 | 0 |
| December 2, 1947 | 5.0 | 15.9 | 44 | 55,000 | 6,400 | 60 | 28 | 12 | 0 | 0 |
| March 5, 1948... | 4.4 | 13.3 | 41.5 | 44,000 | 7,450 | 62 | 29 | 9 | 0 | 0 |

* A few "irritation" lymphocytes were noted on this day.

On the basis of the clinical findings and the blood values the diagnosis of polycythemia vera was confirmed. (Table 1 and Fig. 1.) Phlebotomy was done on May 13, 1947, and the patient was asked to return on May 28th, at which time she was given approximately 8.4 mc. of radioactive phosphorus intravenously and was allowed to return to her home. About five weeks later the patient's personal physician called and said that the patient "looked as if she had been in an automobile accident" with extensive ecchymoses and purpuric lesions. She was hospitalized on July 9, 1947, at the Simpson Memorial Institute and stated that she had apparently been improving until late in June when she had noted tiny red blotches on her lower extremities followed in a few days by the spontaneous appearance of large bruises. She also noted the onset of almost continuous gradual bleeding

from her nose. Examination showed very extensive petechiae and large ecchymoses, the latter being largely limited to the extremities. There were multiple areas of oozing from the mucous membranes of both sides of the nose. The remainder of the examination was essen-

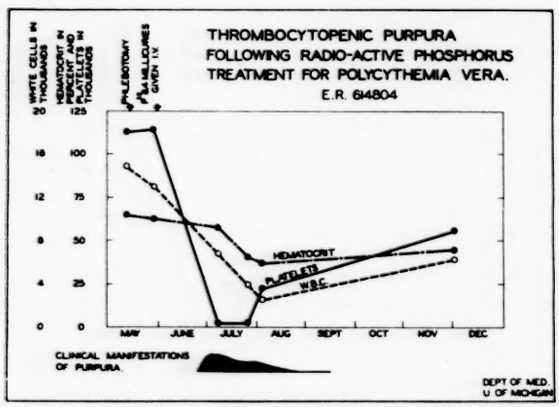


FIG. 1. Graphic representation of hematologic changes.

tially as it had been two months earlier except for some decrease in the general erythema.

Blood studies showed some fall in red cell values and a distinct decrease in the white cell count. Platelets were almost absent. Clotting time (Lee-White) was five minutes; bleeding time (Duke) was ++++ prolonged (more than twenty minutes). There was no clot retraction in three hours. The tourniquet test was strongly positive. Sternal puncture was done. There was a cellular marrow with developing erythrocyte and granulocyte forms present in normal ratio showing essentially normal distribution of various stages of maturity. Developing eosinophiles were fairly prominent. Granulocytic forms showed slight vacuolation but no pronounced basophilic granulation of the cytoplasm. Plasma cells were relatively increased in number and included some large multinucleated forms. Megakaryocytes were present in approximately normal numbers but practically all of them showed striking morphologic changes. They were extremely variable and some could be identified as megakaryocytes only because there were transitional forms between these extremely bizarre structures and megakaryocytes of unequivocal identity. In many the cytoplasm appeared to be fragile, projecting out in long formless wisps. In some it appeared more dense, with multiple vacuoles and in some it was a distinct, well formed meshwork. There were some condensations in the cytoplasm which may have represented abnormal maturation of large platelet forms. The nuclei of the megakaryocytes lacked lobulation but there were frequently two or more nuclei per cell. The chromatin tended to form a coarse, loose pattern in many of these nuclei. (Figs. 2 to 4.)

The patient was kept at bed rest and given repeated doses of from 100 to 250 cc. of blood plasma intravenously. There appeared to be some temporary improvement in the nasal bleeding with each injection of plasma. It was thought that loss of blood from the nose was sufficient to contribute significantly to the fall in red cell values. No transfusions of whole blood were given. There were repeated crops of petechiae with a general tendency toward a diminution in number. Over a period of three weeks there was gradual decrease in the ecchymoses while the nasal oozing became intermittent and finally stopped. The patient returned home on August 7, 1947. She was seen again three weeks later when she appeared to be getting along well; there were no purpuric manifestations. However, the tourniquet test was still positive in moderate degree.

On December 2, 1947, the patient was again seen for follow-up. She was feeling entirely well, with good general strength. The spleen was not palpable. There were no purpuric manifestations but the tourniquet test showed slight residual increased capillary fragility. Clotting time was seven minutes. Bleeding time five and one-half minutes. Clot retraction was good in one hour. Sternal puncture was repeated and again showed a cellular marrow with normally developing erythrocyte and granulocyte elements. The proportion of developing erythrocytes to granulocytes was approximately 1:2. Megakaryocytes were present in at least normal numbers. Although a minority of these showed the unusual morphology seen in the first marrow study, most were essentially normal. Many of them appeared rather young and had a relatively small amount of cytoplasm. Only rarely was definite evidence of platelet maturation noted in the cytoplasm. (Fig. 5.)

The most recent out-patient visit was made on March 5, 1948. The patient had been feeling very well but had had a recurrence of petechiae over the upper extremities late in February when she had been very active doing house cleaning. These petechiae had cleared spontaneously. The examination was otherwise the

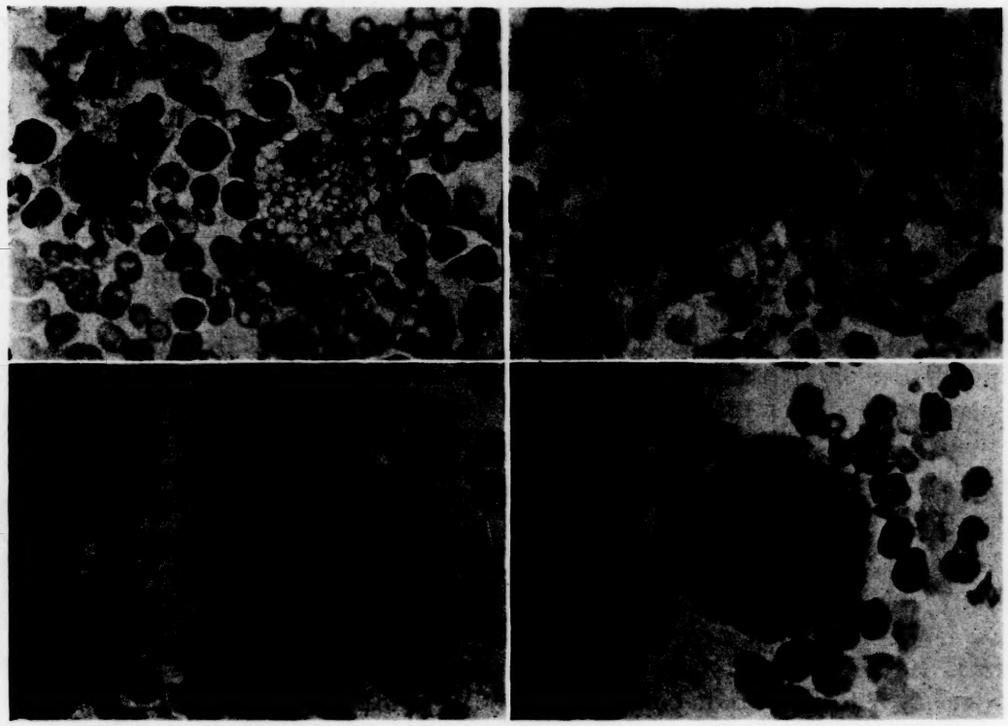


FIG. 2. Photomicrograph of sternal marrow obtained during acute purpuric episode and showing two very abnormal cells believed to be megakaryocytes.
FIGS. 3 and 4. Atypical megakaryocytes from the same sternal puncture.
FIG. 5. From material obtained eight months later, after platelets had increased. This shows a relatively normal megakaryocyte.

same as in December, 1947. The tourniquet test was slightly less positive than it had been at that time.

The blood values shown in Table 1 were determined by standard methods. Platelets were counted on carefully spread blood films prepared on cover slips previously spread with cresyl blue and later stained with Wright's stain. The platelet values were determined by counting the number of platelets seen per 1,000 red cells and calculating the total on the basis of simultaneously done red counts. During the recovery phase many of the platelets were very large.

## COMMENTS

This patient had typical polycythemia vera but even before treatment was given the platelets were somewhat below the average normal values and distinctly below the increased levels usually present in polycythemia vera. X-ray therapy which had been given about four months before the $P^{32}$ undoubtedly had some depressing effect upon the bone marrow and may have been, in part, the cause for the mild thrombocytopenia which was present when the patient was first seen by us. However, there had been enough time for manifestation of the maximal effect of this x-ray therapy before the radioactive phosphorus was given. This dosage of radioactive phosphorus had not been found excessive in other patients with the same disease. It is believed that the profound thrombocytopenia which developed in this patient was an exaggeration of the usual decrease in platelets caused by $P^{32}$ treatment. Probably the severity of the thrombocytopenia was conditioned by a pre-existing tendency toward inadequacy of platelet formation which had not been clinically apparent. There are undoubtedly other factors which influence individual variations in response.

The experience with this patient as well as the course of other patients treated by us suggests that individuals who have low platelet counts before therapy are more

likely to suffer severe thrombocytopenia after $P^{32}$ is given than are those who have normal or high platelet counts at the outset. Thus it would appear that this form of treatment should be used with caution, if at all, in patients with decreased platelets.

Although the number is limited, all reported patients with this complication of radioactive phosphorus treatment have made spontaneous recoveries from thrombocytopenia unless the underlying blood disorder contributed to a fatal outcome. However, there seems little doubt that fatal hemorrhage might result from radioactive phosphorus alone if the dose were really excessive.

The striking morphologic changes noted in the megakaryocytes of the marrow during the purpura were probably a result of the radioactive phosphorus. It is unfortunate that no pretreatment sternal puncture was done. If the megakaryocyte changes had been shown to be absent before treatment, this would lend support to the supposition that they were due to the $P^{32}$. There is little doubt, however, that the abnormality of the megakaryocytes was associated with the thrombocytopenia and the latter occurred at about the same length of time after treatment as in other reported cases of purpura induced by radioactive phosphorus. If further experience shows that these megakaryocyte changes are characteristic in irradiation-induced thrombocytopenia, they may be of considerable interest and occasionally may be of value in diagnosis. The morphology of these megakaryocytes is entirely different from that seen in idiopathic thrombocytopenic purpura.

There is no established treatment for this type of irradiation-induced purpura. Our patient was given rest, plasma and symptomatic measures. Blood transfusions would undoubtedly be helpful in combating anemia and might cause temporary improvement in capillary permeability. Artifically induced phosphorus diuresis might increase the excretion of the radioactive material but would probably be of little practical value after the onset of purpura. In view of the bone marrow picture and the lack of evidence indicating that the spleen plays a role in this type of thrombocytopenia it is doubtful that splenectomy would be of value.

## SUMMARY

A patient who had polycythemia vera was given radioactive phosphorus and developed severe thrombocytopenic purpura associated with prominent changes in the appearance of the megakaryocytes.

It is suggested that radioactive phosphorus should be used with caution especially in patients who already have thrombocytopenia.

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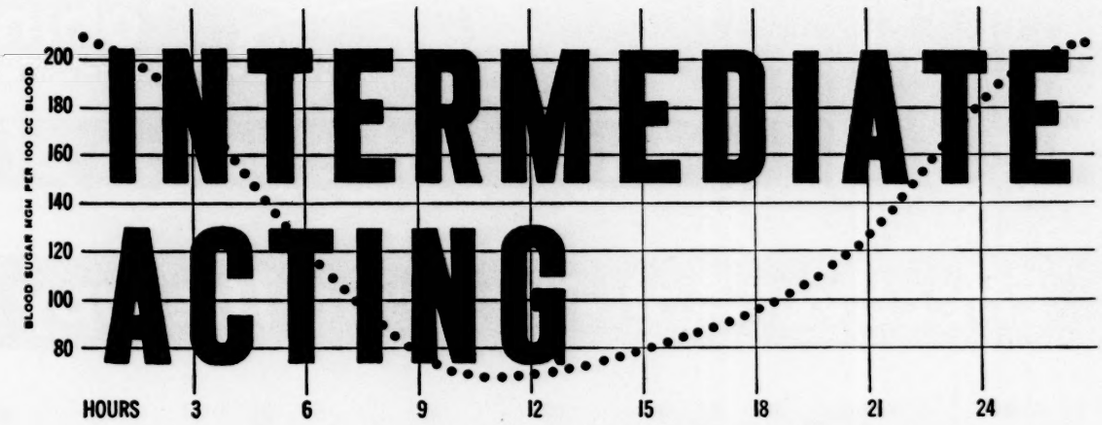


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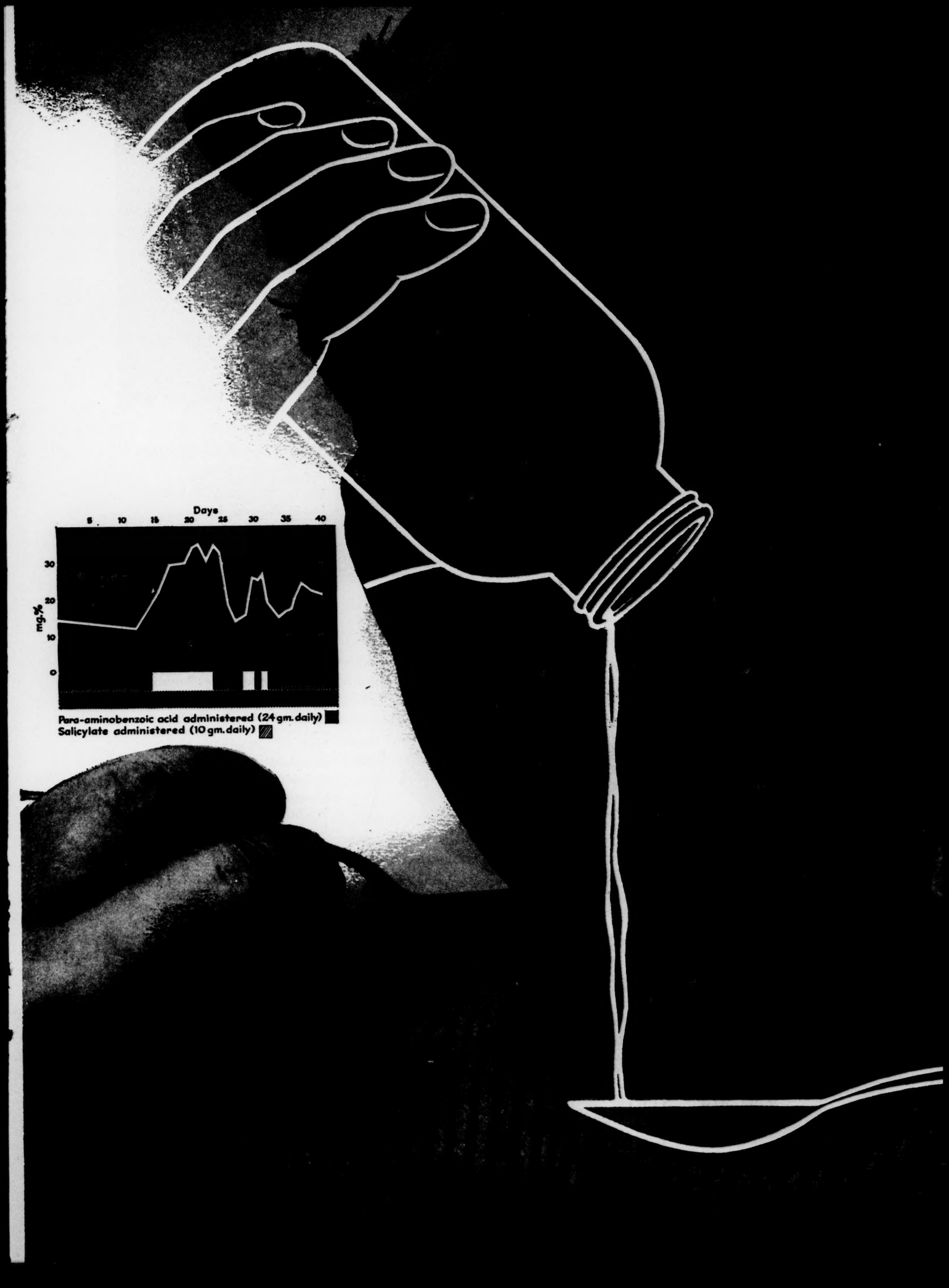
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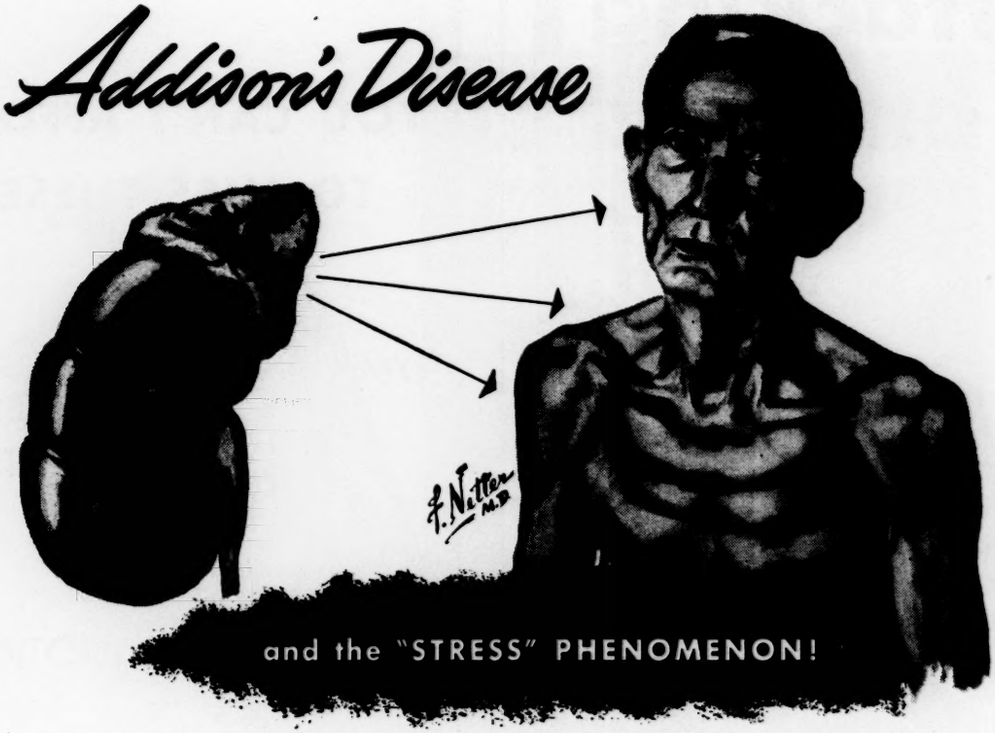


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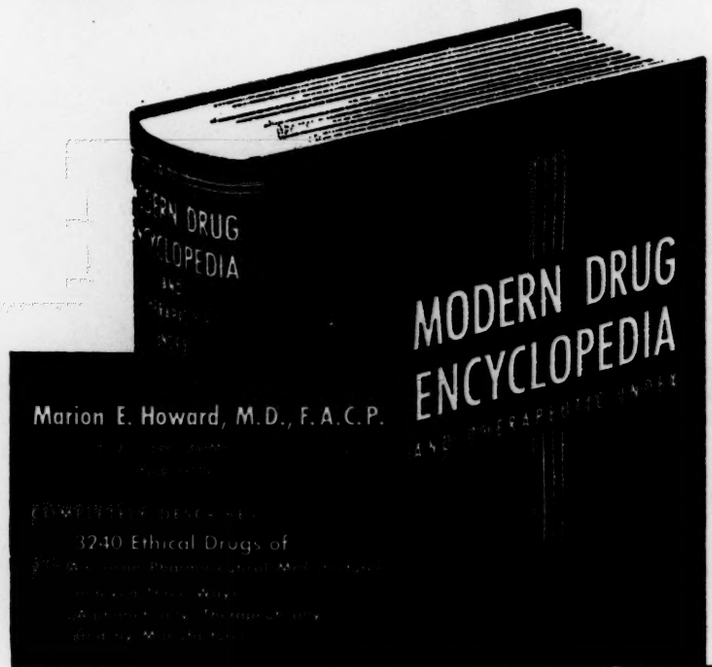


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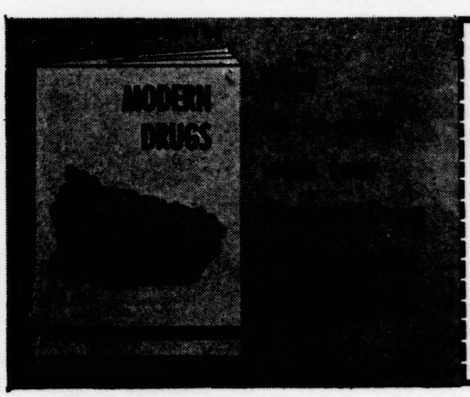


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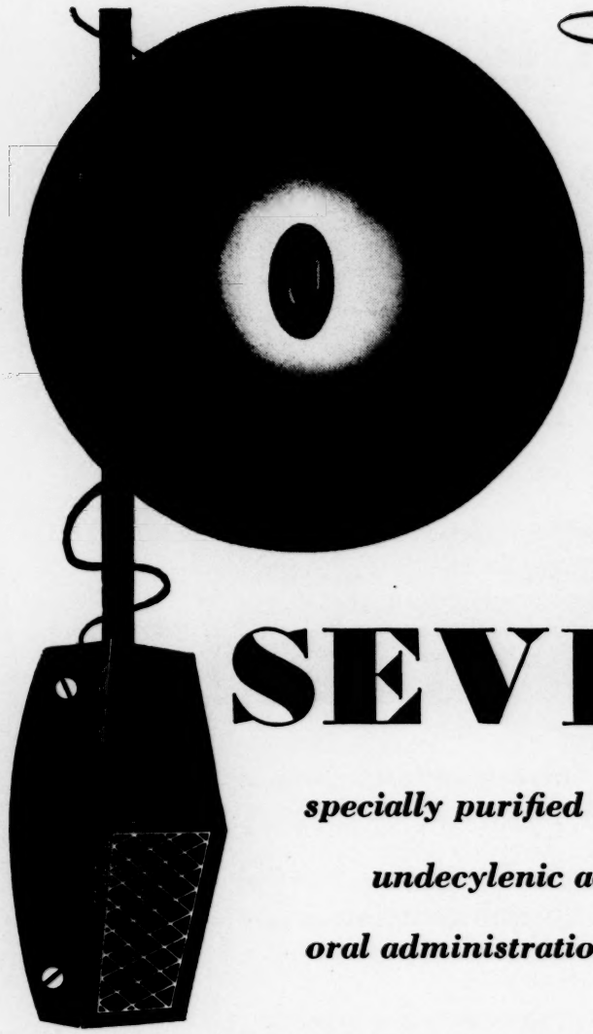
| CALCIUM | 1.12 Gm. | VITAMIN C | 30.0 mg. |
| PHOSPHORUS | 0.94 Gm. | VITAMIN D | 417 I.U. |
| IRON | 12 mg. | COPPER | 0.5 mg. |

***Based on average reported values for milk.**

**Two kinds, Plain and Chocolate Flavored. Serving for serving, they are virtually identical in nutritional content.**



*Schering*

***is pleased to announce that it has made available for use in the treatment of***

## PSORIASIS

# SEVINON

***specially purified undecylenic acid for oral administration***

Attention has recently been drawn to "an interesting approach"[1] to the control of psoriasis and neurodermatitis. Perlman[2] has reported that following the oral use of undecylenic acid, psoriasis was relieved completely in 3 out of 17 patients, and was partially relieved in the remainder. "Relief of itching is sometimes noticed as early as two days after institution of treatment . . . undecylenic acid seems to hold a great deal of promise in the improvement and possible prevention of recurrences of psoriasis and neurodermatitis."[2]

SEVINON* is available in gelatin capsules containing 0.44 Gm. undecylenic acid, highly purified for oral use. The dosage employed by Perlman[2] corresponds to 5 to 6 capsules three times daily by mouth, continued in some cases for as long as six months.

1. Undecylenic Acid and Psoriasis, editorial, J.A.M.A. 139:460, 1949.
2. Perlman, H. H.: J.A.M.A. 139:444, 1949.

*SEVINON trade-mark of Schering Corporation

*Schering* CORPORATION · BLOOMFIELD, NEW JERSEY

SEVINON

SCHERING

# not just resin
# not just mucin

# but → RESMICON®

## mucoprotective acid-adsorbent for peptic ulcer therapy

— relieves pain and promotes healing in peptic ulcer
— relieves distress in hyperacidity

**RESMICON'S** anion-exchange polyamine resin combats acidity by a new—non-chemical—principle. It physically adsorbs acid radicals. In the stomach resin rapidly inactivates HCl and inhibits pepsin with complete freedom from side effects.

**RESMICON'S** natural gastric mucin protects the gastric mucosa. Clinicians have amply demonstrated its value in peptic ulcer therapy. But mucin alone is limited by its weakness as an antacid and by the large and frequent dosage required.

**RESMICON,** uniting resin and mucin, is an outstanding agent for the effective treatment of peptic ulcer and hyperacidity.

Whittier
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